

**DEVELOPING THE EVIDENCE BASE FOR A DIGITAL INTERVENTION TO  
ENHANCE ADHERENCE TO MEDICATION IN PEOPLE WITH HYPERTENSION**

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## **Declaration**

I declare that this thesis has not been submitted as an exercise at this or any other university.

I declare that this thesis is entirely my own work.

Signed: \_\_\_\_\_

Eimear Morrissey

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## Abstract

**Background.** Hypertension is a chronic condition in which the blood vessels have persistently raised pressure. It is a major modifiable risk factor for both cardiovascular and cerebrovascular disease. Hypertension is estimated to affect one billion people worldwide and is therefore a global health challenge. The pharmacological treatment of hypertension has led to substantial benefits in the prevention of morbidity and mortality from cardiovascular and cerebrovascular disease. However, despite their established efficacy, there is a significant problem of non-adherence to anti-hypertensive medications in those diagnosed and prescribed this treatment; therefore the effectiveness of current medications is sub-optimal. Traditionally, intervention to enhance adherence to anti-hypertension have been delivered face to face or over the telephone. Digital interventions, such as those delivered via smartphone apps, offer a new, scalable and potentially cost-effective way to improve adherence to anti-hypertensive medications. However as the growth of these platforms has been relatively recent, little is known about the development, acceptability, usability and feasibility of these type of interventions.

**Aim.** The aim of this research is to develop the evidence base for a digital intervention to enhance medication adherence in people living with hypertension.

**Methods.** The studies conducted in this research were based on the development phase of the UK Medical Research Council Framework for developing complex interventions. In the first study a systematic review and meta-analysis was conducted to identify evidence base related to interventions to enhance adherence in hypertension. In order to characterise the technology base, the second study was a content analysis of smartphone apps to enhance medication adherence. Two qualitative studies were then conducted, the first with GPs and the second with patients with hypertension in order to explore their thoughts and

views around using a smartphone app to manage their medication adherence. Thematic analysis was conducted in both these studies.

**Findings.** The systematic review found tentative evidence to suggest that medication adherence interventions significantly lower blood pressure values. However, there was substantial heterogeneity amongst the included RCTs and many potential biases as the number of low risk of bias studies was limited. The content analysis of existing mobile phone applications highlighted a lack of behavioural theory and evidence integrated into commercially available medication adherence apps. Participants in both qualitative studies (GPs and patients with hypertension) could see benefit as well as expressing concern about a digital intervention such as a smartphone app. Both parties felt it could be empowering but also had reservations about the possible anxiety inducing nature of excessive engagement with the intervention.

**Conclusion.** The findings of this research contribute to insights in relation to the development of a digital intervention to enhance medication adherence in hypertension. The use of theory, systematic review and qualitative work means that this research was an appropriate enhancement of the evidence base and provides a platform for future intervention development.

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## **List of Abbreviations**

AHA	American Heart Association
BCT	Behaviour Change Technique
BCTTv1	Behaviour Change Technique Taxonomy version 1
BP	Blood Pressure
CORE-Q	Consolidated Criteria for Reporting Qualitative Research
CS-SRM	Common Sense Self-Regulation Model
DBP	Diastolic Blood Pressure
DI	Digital Intervention
GP	General Practitioner
HCPs	Health Care Providers
IDI	Interactive Digital Intervention
IHF	Irish Heart Foundation
NICE	National Institute for Health and Care Excellence
MEMS	Medication Event Monitoring System
MRC	Medical Research Council
PRISMA	Preferred Reporting Items for Systematic Reviews & Meta Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomised Controlled Trials
SBP	Systolic Blood Pressure
TDF	Theoretical Domains Framework
TILDA	The Irish Longitudinal Study of Aging
WHO	World Health Organisation

## **1. Introduction**

### **1.1 Chapter overview**

In this chapter the relevant background to the research will be described. This will include information related to the current scientific understanding of hypertension, self-management of hypertension with an emphasis on adherence to anti-hypertensive medications and the relevance of these factors in developing the evidence base around digital interventions to enhance adherence to anti-hypertensive medication. The rationale for the current research will then be made and finally an outline for this thesis will be summarised.

### **1.2 Hypertension**

Blood pressure (BP) is a measure of the pressure which blood places against the walls of blood vessels during circulation. It is typically measured using two numbers, systolic blood pressure (SBP; the pressure in the blood vessel when the heart beats, normal values ~120mmHg) and diastolic blood pressure (DBP; the pressure in mmHg in the blood vessel when the heart rests between beats, normal values ~80mmHg). When SBP rises above 140mmHg or DBP above 90mmHg, the patient is deemed to have high blood pressure (i.e. hypertension), which places stress on the heart for the circulation of blood in the body (Irish Heart Foundation, 2018). These guidelines are currently in dispute however, with recent reports from the American Heart Association (AHA) suggesting that the hypertension cut off should be lowered at 120mmHg/80mmHg in order to raise awareness of hypertension and focus initiation of treatment (Muntner et al., 2017).

This new diagnostic standard illustrates the serious nature of hypertension as an illness. Epidemiologic studies demonstrate that cardiovascular disease events (e.g. stroke, heart failure, myocardial infarction, unstable angina and coronary heart disease) are associated

with hypertension (Amici et al., 2009; Pini et al., 2008). A key systematic review (Kearney et al., 2005) found it to be the single most important modifiable risk factor for stroke and myocardial infarction in both developed and developing countries. The World Health Organisation (WHO) recognises the contribution of hypertension to both disease and premature death and disability and has called for concerted action on the condition (World Health Organization, 2015). The treatment of hypertension is therefore a key focus of primary and secondary prevention of cardiovascular disease in both economically developed and developing countries. It is estimated that hypertension affects one billion people worldwide and represents a global health challenge (Forouzanfar, Liu & Roth, 2017). Within an Irish context, the Irish Longitudinal Study on Ageing (TILDA) conducted a cross-sectional study of a nationally represented sample of community living adults aged 50 and over from 2009 to 2011 (n = 5857) and found a high prevalence (63.7%) of hypertension among this population (Murphy, 2015).

### **1.3 Anti-hypertensive medication**

There are eight essential medications used to treat hypertension. These include four anti-hypertensive medications (thiazide diuretic, an angiotensin converting enzyme inhibitor, a long acting calcium channel blocker and a beta blocker) and four other multi-purpose medications (metformin, insulin, a statin and aspirin) (World Health Organization, 2015). Depending on the severity of the hypertension, patients may be prescribed one or a combination of these drugs. From the introduction of the first thiazide diuretic over fifty years ago, anti-hypertensive medications have consistently been shown to be effective in reducing blood pressure values (Chobanian, 2009). Placebo-controlled trials have shown that anti-hypertensive medications can reduce the incidence of coronary events by 20-25%, the incidence of stroke by an average of 35-40% and the incidence of congestive heart failure by more than 50% (Neal, MacMahon, & Chapman, 2000). More recent reviews

support these findings e.g. a systematic review and network meta-analysis of each of the different medication types found that all of the agents showed evidence of benefit (Hutton et al., 2014). A Cochrane review by Musini, Tejani, Bassett and Wright (2009) conducted an assessment of all the trials of blood pressure lowering therapy in people with hypertension aged 60 years and over and found that treatment reduced death, strokes and heart attack. Therefore, it is well established that hypertension control through these pharmacological treatments has led to substantial benefits in the primary prevention of morbidity and mortality from cardiovascular disease (Wright & Musini, 2009). As well as evidence of effectiveness, anti-hypertensive medication has been shown to be cost-effective too. A recent systematic review analysed 76 studies across all medicine classes and concluded that all medications were cost-effective when compared to no treatment (Park, Wang, Durthaler, & Fang, 2017).

#### **1.4 Non-adherence to medication**

Despite these well documented benefits, problems still exist in the pharmacological treatment of hypertension. The WHO defines adherence to long-term therapy as “the extent to which a person’s behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider” (Sabaté, 2003). Non-adherence occurs when a patient does not: initiate a new prescription, implement as prescribed, or persist with treatment (Vrijens, Antoniou, Burnier, de la Sierra, & Volpe, 2017). Findings suggest that non-adherence should fall into two separate phenomena; intentional and non-intentional non-adherence (Wroe, 2002). Intentional non-adherence refers to deliberate non-adherence in which the patient chooses to deviate from the medication regime whereas in unintentional non-adherence the non-adherence is a more passive process in which the patient may be forgetful or careless in adhering to the medication regime (Molloy et al., 2014). This may be an over-simplistic

dichotomy and there may be overlap between these categories (e.g., people who have a don't believe their medication is always effective may see it as less salient and may be more likely to forget to take it) however this pragmatic distinction can usefully inform intervention approaches to have their emphasis on individual motivation versus individual capacity/opportunity to take their medications (Clifford, Barber, & Horne, 2008). A cross-sectional study in the US found that both types of non-adherence were present in a hypertensive population although unintentional non-adherence seemed to be more common (Lowry, Dudley, Oddone, & Bosworth, 2005).

The WHO has posited that, in general, there are five dimensions to adherence: condition related factors, health system factors, socio-economic factors, therapy related factors and patient related factors (Sabaté, 2003). While these dimensions are not entirely independent of each other, this serves as a useful means for organising the broad range of factors that can contribute to non-adherence. Two of the most important determinants contributing to poor adherence in hypertension therapies are the asymptomatic and lifelong nature of the disease (both condition related factors). Other factors include side effects of medication (therapy related), complicated drug regimens (therapy related), lack of awareness about hypertension management (patient related), lack of motivation (patient related), forgetfulness (patient related) and challenge to individual patients' health beliefs (patient related) (Dowell, Jones, & Snadden, 2002; Tong, Chu, Fang, Wall, & Ayala, 2016). As condition and therapy related factors are often not amenable or are more difficult to change, patient related factors more frequently offer the greatest potential for intervention.

### **1.5 Non-adherence to anti-hypertensive medication**

As a largely asymptomatic disease, hypertension is sometimes described as being as 'a disease without an illness', presenting a challenge for appropriate adherence to treatment

and engagement with self-care (Holt, Rung, Leon, Firestein, & Krousel-Wood, 2014).

High adherence (defined as medication possession ratio of 80 % to 100%) to hypertensive medications is associated with higher probability of blood pressure control compared with those with medium or low levels of adherence (Bramley, Gerbino, Nightengale, & Frech-Tamas, 2006). Evidence from a number of studies suggests that as many as 50% to 80% of patients prescribed pharmacological antihypertensive therapy have low adherence to their treatment regimen (Elliott, 2008). A population based cohort study in the UK found that one in five newly diagnosed patients with hypertension discontinued all antihypertensive medications by six months, while one in two discontinued all antihypertensive medications by three years (Burke et al., 2006). However, medication adherence in this study was measured by prescription refill records, which assumes patients prescription-refilling patterns correspond with the patient's medication taking behaviour, and so may be an underestimate (Farmer, 1999; Lam & Fresco, 2015). Vrijens, Vincze, Kristanto, Urquhart, and Burnier (2008) conducted a similar cohort study but used medication event monitor system (MEMS) data, which is considered a more robust measure of adherence because it can identify whether adherence is irregular or consistent and can detail the number of daily doses taken or missed (Lam & Fresco, 2015). They found that approximately half of all patients prescribed the medications stopped taking them within one year of the initial prescription. They also found that on any one day, 10% of patients omitted their scheduled dose of medication. Such small deviations can be clinically important as Bailey, Wan, Tang, Ghani, and Cushman (2010) estimated that increasing adherence to antihypertensives by just one tablet per week could reduce the hazard of stroke by 8–9 % and of death by 7 %. According to the WHO, this lack of adherence to antihypertensive medication is the most important cause of failure to achieve BP control (Sabaté, 2003).

As well as a personal cost to health, non-adherence to medication also leads to an economic cost for healthcare, as it leads to increased demands on healthcare resources if a patients' health deteriorates (NICE, 2009). A probabilistic prevalence based model, over a 10-year period, in five European countries (Italy, Germany, France, Spain and England) indicated that if adherence to antihypertensive therapy was increased to 70%, a total saving of €332 million could be achieved (Mennini et al., 2015).

### **1.6 Existing interventions for non-adherence to anti-hypertensive medication**

In primary prevention, a range of interventions to improve adherence to anti-hypertensive medications have been evaluated. These interventions can have multiple components, such as education around the condition and the importance of adherence, skills development, combination pills, blister packs, reminders, motivational interviewing, lifestyle counselling, self-management workbooks, shared decision making, record keeping, provision of practical support and self-monitoring of blood pressure. They can also be delivered in a range of contexts by various healthcare providers (HCPs) such as physicians, nurses and pharmacists. These interventions have had mixed results (e.g. Amado Guirado, Pujol Ribera, Pacheco Huergo, & Borrás, 2011; Matsumura et al., 2012). A systematic review by Schroeder, Fahey, and Ebrahim (2004) examined 58 different interventions to enhance adherence to anti-hypertensive medications. They found such a wide heterogeneity in both the interventions types and outcome measures that they were unable to pool the results. More recently Conn, Ruppap, Chase, Enriquez, and Cooper (2015) conducted a meta-analysis of both randomized and non-randomized studies that targeted anti-hypertensive medication adherence improvement. The results found that 112 intervention vs. control group comparisons had a standardised mean difference effect size of 0.30 (SD 0.08,  $p < 0.001$ ) on measures of adherence. The analysis also revealed that there was considerable statistical heterogeneity in the effects observed across studies ( $I^2 =$

87%), which can be partly explained by heterogeneity in the methodologies employed and in particular the samples studied, the research designs and measures used to assess adherence.

These interventions come from a large range of healthcare practice disciplines (e.g. medicine, pharmacy and nursing). However, within health psychology, there is a particular emphasis on theory, which provides a mechanism to encapsulate existing knowledge about how variations in interventions produce a desired behaviour change (Walsh & Morrissey, 2018). Theories of behaviour can provide explanations regarding the processes that are occurring, and facilitate an understanding of complex situations (Davidoff, Dixon-Woods, Leviton, & Michie, 2015). As theory can provide these kinds of predications and explanations that support the generalisation of findings from past work into future areas of inquiry (Noar & Zimmerman, 2005), health psychology has the potential to play an important role in informing the systematic development and evaluation of complex interventions to improve adherence. Key papers (e.g. Craig et al., 2008; Davidoff et al., 2015; Eiser et al., 2013) argue that the use of theory and the explicit descriptions of its use, are necessary to facilitate the design of interventions to change behaviour. This can contribute to enhanced standardisation in development and evaluation of interventions and contribute to the development of a more cumulative evidence base.

## **1.7 Psychological theory and medication adherence**

### **1.7.1 Dual process model**

Psychological theories of health behaviour and health behaviour change have developed in order to understand and explain medication non-adherence (along with other health behaviours). Within health psychology, the dominant theories of health behaviour change view behaviour as a function of conscious reflection and active decisions (e.g. the theory

of planned behaviour (Ajzen, 1991); social cognitive theory (Bandura, 1986)). These theories often assume that maintenance will be an outcome of the successful initiation (Phillips, Cohen, Burns, Abrams, & Renninger, 2016). A meta-analysis by Conn, Enriquez, Ruppap, and Chan (2016) on the use of theory in medication adherence research found that these types of social cognition theories are the most commonly used, perhaps as a result of this emphasis on conscious reflection and active decision making. However, these theories fail to adequately account for the environment, which acts as a cue for much of human behaviour and these behaviours are often carried out without active reflection and decision making (Presseau et al., 2014). A newly developing literature calls for consideration of non-conscious influences on behaviour as well as the well-established reflective processes (Hofmann, Friese, & Wiers, 2008). Strack and Deutsch (2004) reflective-impulsive model is an example of these dual process models. They propose that the reflective process is the effortful process of which the individual is consciously aware and in control, carrying out the behaviour based on conscious deliberation. In contrast, the impulsive process requires little cognitive capacity and operates quickly and automatically requiring minimal effort and is the default process in determining behaviour. Given this default role, the impulsive process drives behaviour unless there is a capacity and need for conscious decision making. This can be seen in Figure 1.1.

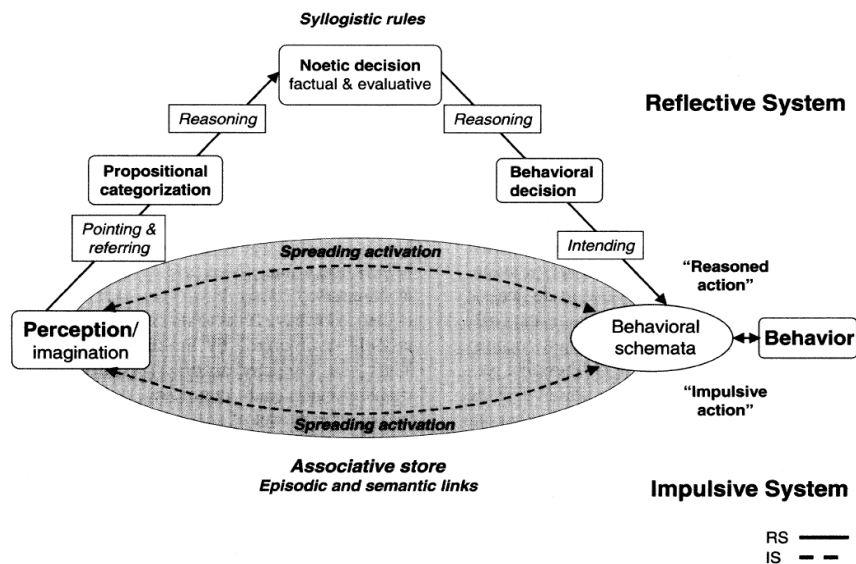


Figure 1.1. The reflective impulsive model

A dual process model may be more suitable than a traditional social cognition model for medication adherence research as daily medication taking involve impulsive processes (i.e. habit) as well as reflective processes. While attempts to improve intentional non-adherence can target reflective processes such as treatment beliefs, and this may be helpful in the initiation stage of medication adherence, it is more likely that the persistence of the behaviour and unintentional (non)adherence will be influenced by the impulsive system.

### 1.7.2 The Common Sense Self-Regulation model

The common sense self-regulation model (CSM-SR; Leventhal, Brissette, & Leventhal, 2003) incorporates elements of other health behaviour theories and has been used in several illness contexts to predict patients' medication adherence (Leventhal, Weinman, Leventhal, & Phillips, 2008). It posits that an individual's illness identity, causes, timeline, consequences and control beliefs affect their behaviours in response to a health threat, including their adherence to the prescribed medication (Phillips, Leventhal, & Leventhal, 2013). Control beliefs refer to the degree of control the patient thinks they have, the doctor has and the treatment has. These treatment beliefs, particularly those regarding the

treatment itself (i.e. belief in the necessity of and concerns regarding the treatment) have been shown to predict medication adherence (Horne & Weinman, 1999). The Necessity Concerns Framework (NCF) suggests relationships between two separate dimensions—patients' necessity beliefs and concerns regarding medication—and between these two predictors and medication adherence. The NCF states that patients implicitly weigh the costs against the benefits of taking a medication when deciding whether or not to adhere to it and that medication adherence will be greater the more patients' beliefs in the necessity of the medication exceed their concern (Horne & Weinman, 1999). The Beliefs about Medication Questionnaire (BMQ) was developed to assess these beliefs. A meta-analysis of 94 publications using the BMQ by Horne et al. (2013) showed that the Specific Necessity Beliefs measure was positively and consistently related to adherence, and Specific Concerns scores were consistently and negatively related to adherence. However, work by Verplanken (2006) has suggested that these treatment beliefs may be more predictive in the short term than in the long term implying that they may play a larger role in the initiation rather than the maintenance of adherence behaviour. Evidence shows that treatment beliefs are associated with intentional non-adherence as these beliefs can represent a reflective choice on how to behave (O'Carroll, Whittaker, Hamilton, Johnston, Sudlow, & Dennis, 2010; O'Carroll, Chambers, Dennis, Sudlow, & Johnston, 2014). This is particularly salient in hypertension as it is asymptomatic and patients with hypertension may choose not to take their medication as they do not feel ill (Anthony, Valinsky, Gabriel, & Varda, 2012).

### **1.7.3 Habits**

A possible critical influence on the maintenance of long term adherence is habit. Habits are a specific form of cue-response association formed in memory as a consequence of

repeated performance of a particular action in response to a particular cue context (Wood & Rünger, 2016). Once a behaviour is more strongly influenced by the impulsive system and becomes habitual it does not require reflection or deliberation on reasons, because habits are automatically triggered by conditioned contextual cues e.g. a person may take their medication i.e. the behavioural response, in the morning and evening after the cue of brushing their teeth (Gardner, 2015). Habits are thought to function in two ways; by prompting frequent performance when associated with commonly encountered cues and by dominating over intentions in regulating action (Hall & Fong, 2007). Therefore, habitual treatment related actions are more likely to be maintained in the future than non-habits which are subject to changes in the reflective system, such as attitudes and goals. Accordingly, habits are theoretically important for long-term medication adherence and have been found to predict this behaviour in many conditions (Rothman et al., 2015), including hypertension (Bolman, Arwert, & Völlink, 2011; Phillips et al., 2013). Indeed, Phillips et al. (2013) found that patients with hypertension who had been prescribed a medication for multiple years were most adherent when they reported having a habit or routine for taking their medication; if medication use was associated with consistently experienced environmental cues, taking medication was habitual and the patient was highly adherent (not just to the day, but to a specific time of day). This habit strength was the strongest predictor of all adherence measures, explaining 6 – 27% incremental variance in adherence. They concluded that in these patients' who had been taking the medication for some time the commonly investigated factors such as treatment-related beliefs, presence or absence of barriers to adherence, and experiences that the treatment worked as expected were not the essential ingredients.

#### **1.7.4 Extended CS-SRM model**

Leventhal, Phillips, and Burns (2016) have stated that the CS-SRM is constantly evolving and research should be conducted on the automatic or habitual processes involved within it. Phillips et al. (2016) have proposed extending the current CS-SRM inspired adherence research to emphasise behavioural habit strength as a medication adherence factor important for long term maintenance, as previous research using the CS-SRM has focused more strongly on cognitive representations of treatment. This proposal was based on a previous study of theirs (Phillips et al., 2013) which found that hypertensive patients' beliefs predicted intentional non-adherence and habit strength predicted unintentional non-adherence. While their study on medication adherence among patients with type 2 diabetes did not support the extended model, they have called for further refining of the CS-SRM theory regarding the processes required for habit development. A recent study by O'Carroll, Chambers, Dennis, Sudlow, and Johnston (2013) used temporal self-regulation theory to develop an intervention to enhance medication adherence in stroke survivors. Temporal self-regulation theory can account for both intentional and unintentional non-adherence as it incorporates both reflective (based on belief or value systems) and automatic (based on past experiences or environmental cues) behavioural processes (Hall & Fong, 2007). The intervention consisted of two components – reflective behaviour was addressed by examining and modifying the patients' mistaken beliefs and automatic behaviour was targeted using implementation intentions. Participants in the intervention group had 10% greater adherence to scheduled doses of medications and reductions in concerns around medication (O'Carroll et al., 2014). These findings support the idea that interventions for medication adherence should target both reflective and automatic systems.

## **1.8 Digital interventions**

Recent years have seen a proliferation of information and communication technology in everyday life. Such technologies have the potential to profoundly influence behaviour. A recent survey has reported that most Irish people own or have access to a smartphone, laptop and tablet; 86%, 80% and 60% respectively (Deloitte, 2016). Therefore, the use of mobile technology (that which can be carried by the user) is common in Ireland, with the smartphone being the main point of access to the digital domain. The usage of this technology is also high, with over 60% of Irish users checking their smartphones within 15 minutes of waking and continuing to use them throughout the day (Deloitte, 2016).

Popularity, mobility and technological capabilities make these mobile technologies appropriate for providing individual level support to health consumers (Free et al., 2013) and this has led to an increase in health interventions being delivered through digital means. Digital interventions (DIs) are behaviour change interventions that involve, not necessarily exclusively, computer technology or digital encoding of information. They included text messaging, email, body and environment sensors, messaging programmes, email, websites, whole computer systems and perhaps most commonly, smartphone applications (apps) (West & Michie, 2016).

DIs in healthcare offer tremendous potential to manage, monitor and improve patient health and substantial evidence to support this is beginning to accumulate in the context of chronic illness (Morton et al., 2017). There are several advantages to using a DI rather than, or in conjunction with a traditional human-delivered intervention. They can be significantly cheaper to roll out, highly personalised and interactive, can deliver information in a way that is engaging and rewarding and can adapt to users' needs (West & Michie, 2016). A DI can be accessed in real-life environments where the user is making decisions about their health and encountering barriers and facilitators to health related

behaviour change as mobile devices such as smartphones tend to be with the user all day (Dennison, Morrison, Conway, & Yardley, 2013). A DI can easily incorporate the sharing of health or behavioural data with healthcare professionals or family due to the connectedness of a smartphone (Patrick, Griswold, Raab, & Intille, 2008). A particularly critical advantage of DIs is that they can deliver intervention content with a high degree of fidelity. Fidelity refers to the degree to which an intervention happened in the way the investigators intended it to (Carroll et al., 2007). In human-delivered interventions it is often found to be poor (<55%) (e.g. Hardeman et al., 2008; Tober et al., 2008) leading to difficulties in the interpretation of intervention outcomes (Lorencatto, West, Christopherson, & Michie, 2013). The nature of a DI circumvents the delivery part of this problem.

However, there are some drawbacks to DIs too; the development can be costly, frequent updating is needed and most importantly, they cannot fully integrate all the benefits of a human-to-human interaction (West & Michie, 2016). This lack of human support can also lead to lower engagement and high levels of drop out from DIs (Kohl, Crutzen, & de Vries, 2013). It is therefore important that the perspectives of the users are fully taken into account when deciding what type of intervention to develop (Yardley, Morrison, Bradbury, & Muller, 2015).

The feasibility and potential for DIs to effect change in health-related outcomes have been established for a variety of health issues (Lustria et al., 2013; Webb, Joseph, Yardley, & Michie, 2010). Several Cochrane Reviews have investigated DIs and found some evidence of effectiveness for a variety of health issues, including smoking cessation (Taylor et al., 2017; Whittaker, McRobbie, Bullen, Rodgers, & Gu, 2016), reduction of alcohol consumption (Kaner et al., 2017), weight loss (Wieland et al., 2012) and management of chronic pain (Eccleston et al., 2014; Fisher, Law, Palermo, & Eccleston, 2015). Other

systematic review have examined the impact of DIs focused on self-management of chronic conditions such as diabetes (Pal et al., 2014), cardiovascular disease (Pfaeffli Dale, Dobson, Whittaker, & Maddison, 2016) and asthma (Morrison et al., 2014) and have found small benefits to illness outcomes. However, all of these reviews caution that their findings are tentative and further research is needed.

A meta-ethnography by Morton et al. (2017) examined several different types of DIs across a range of chronic conditions, including asthma, heart disease and hypertension. The review included both patients and HCPs' experiences of using self-management DIs. Patients felt that DIs facilitated self-management of their condition as they were better able to understand, make decisions about their health and engage with the HCP in a meaningful way. HCPs saw benefit in being able to track the patients' physiological data over time, leading to improved clinical control. Many DIs contain a self-monitoring component and visualising health data in the context of behaviours such as physical activity medication adherence, promoted patients' perceived control of their illness and enabled them to perceive meaning in their health readings (Morton et al., 2017). Several studies in the review suggested that perceiving a relationship between these behaviours and the physiological data motivated the patients to continue to engage in self-management.

### **1.9 Digital interventions for hypertension**

It is possible that DIs could be effective in enhancing adherence to anti-hypertensive medication. A Cochrane review on medication adherence interventions by Nieuwlaat et al. (2014), recommended that adherence interventions using information and communication technologies needed to be further explored. McLean et al. (2016) conducted a systematic review of interactive DIs (IDIs; web-based packages delivered by computer or phone that can combine health information with decision support and help inform behaviour change

in patients) to promote self-management (including medication adherence) in hypertension. Their meta-analysis of 7 RCTs found a significant reduction in BP values, but they acknowledge a high risk of bias in the studies. A meta-analysis by Liu et al. (2013) on internet delivered interventions to reduce BP identified 13 trials and again, found a significant reduction in BP values. However, this study was done in 2013, before smartphones were as ubiquitous as they are today and so the internet-delivered interventions were most likely accessed by laptop or computer.

Mann et al. (2014) argued that digital interventions based on a mobile device are a potentially powerful modality for hypertension control. Along with the usual listed advantages of DIs, their rationale included reasons such as wireless devices which can collect patient data (e.g. blood pressure) can be easily integrated into digital intervention platforms such as smartphones, and they can embed alerts and reminders for medication taking. Indeed a content analysis of smartphone apps for hypertension management by Kumar, Khunger, Gupta, and Garg (2015) found that the most downloaded apps typically contained a BP tracking function through a wireless BP monitor alongside a pill reminder. As seen in the meta-ethnography by Morton et al. (2017), this type of tracking of physiological data can lead to greater engagement with adherence behaviours. It is possible that seeing this data impacts the patients' treatment related beliefs as illustrated in the CS-SRM (Leventhal et al., 2003) which is a predictor of health behaviour change. As discussed earlier, another crucial component of the maintenance of behaviour is automaticity. Mobile based reminders could possibly provide the cues that are needed for a behaviour to transfer to habit (Gardner, 2015). Therefore a DI based on the components of the extended CS-SRM could possibly be an effective way to enhance adherence to anti-hypertensive medication.

## 1.10 Overall aim

The overall aim of this research was to develop an evidence base for a digital intervention to enhance medication adherence to anti-hypertensive medications. The research question for each study conducted in this research and corresponding papers are outlined below.

### 1.10.1 Research questions and thesis outline

Study 1: What is the effectiveness of adherence interventions for hypertension on blood pressure control and medication adherence and are specific barriers and facilitators associated with the observed effect sizes?

- Morrissey, E. C., Durand, H., Nieuwlaat, R., Navarro, T., Haynes, R. B., Walsh, J. C., & Molloy, G. J. (2017). Effectiveness and content analysis of interventions to enhance medication adherence and blood pressure control in hypertension: A systematic review and meta-analysis. *Psychology and Health, 32*(10), 1195-1232. doi: 10.1080/08870446.2016.127335

Study 2: Are smartphone apps for medication adherence using established Behaviour Change Techniques?

- Morrissey, E. C., Corbett, T. K., Walsh, J. C., & Molloy, G. J. (2016). Behavior Change Techniques in Apps for Medication Adherence: A Content Analysis. *American Journal of Preventive Medicine, 50*(5), e143-e146. doi: 10.1016/j.amepre.2015.09.034

Study 3: What are GPs' perspectives of smartphone apps to support medication adherence in patients with hypertension?

- Morrissey, E. C., Glynn, L. G., Casey, M., Walsh, J. C., & Molloy, G. J. (2017). New self-management technologies for the treatment of hypertension: general

practitioners' perspectives. *Family Practice*, cmx100-cmx100. doi:  
10.1093/fampra/cmx100

Study 4: What are patients with hypertension's perspectives on smartphone apps to support adherence to anti-hypertensive medication?

- Morrissey, E. C., Casey, M., Glynn, L. G., Walsh, J. C., & Molloy, G. J. (in press). Smartphone apps for improving medication adherence in hypertension: patients' perspectives. *Patient Preference and Adherence*.

## **2. Methodology**

### **2.1 Chapter overview**

The aim of this chapter is to outline the overall design of this research. The aims of each study within the research will be presented. A description of the methods used to address the aim of each study will be provided with a discussion of the background and justification for their use. Finally, the ethical issues associated with this study will also be addressed.

### **2.2 Aims and objectives of this research**

The primary aim of this research was to develop an evidence base for a digital intervention to enhance medication adherence to anti-hypertensive medications. Quantitative and qualitative methods were used to develop the evidence by integrating data from the existing literature and existing technology with perspectives of the key stakeholders in relation to the topic of anti-hypertensive adherence.

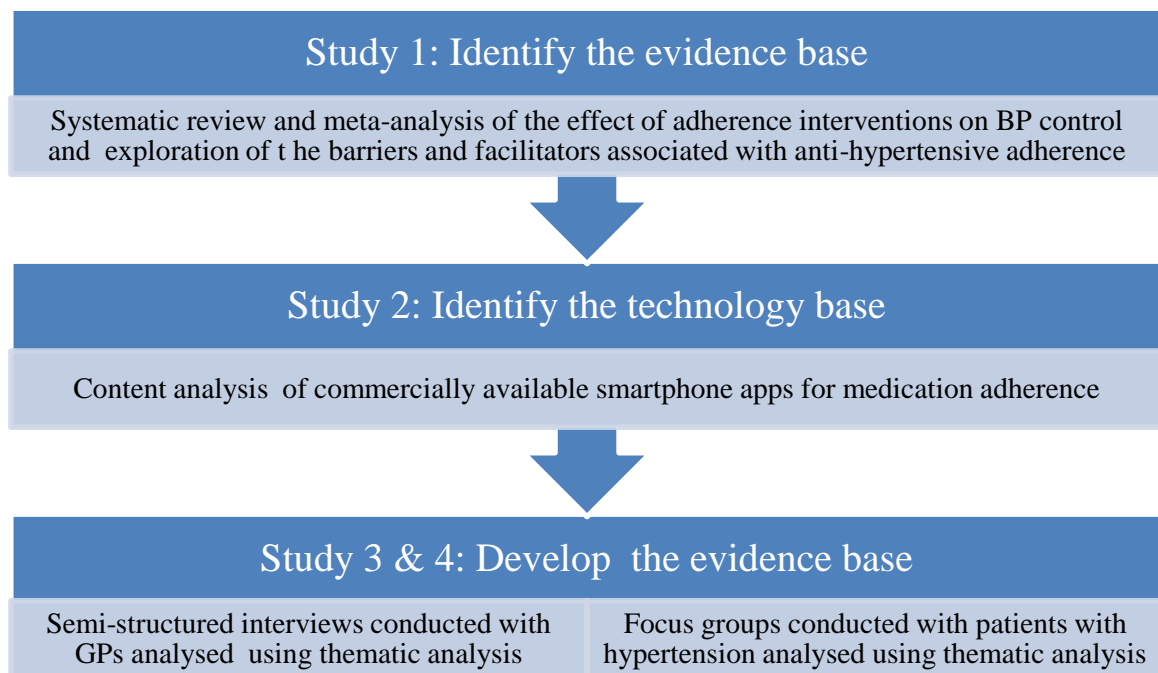
### **2.3 Overview of study design**

The first step of the Medical Research Council (MRC) Framework for the development and evaluation of complex interventions (Craig et al., 2008) is identifying the evidence base. This involves identifying what is already known about similar interventions and the methods that have been used to evaluate them.

Typically quantitative methods, such as a systematic reviews and meta-analyses are used to achieve this aim. These methods often provide insight into the intervention components that have to the potential to be effective but do not offer an insight into which components are likely to be considered useful or feasible by the target population (Yardley et al., 2015). Qualitative research with key stakeholders can provide a deeper understanding of these needs. In fact, Yardley et al. (2015) argue that qualitative research is of particular

importance to the development of digital interventions as people typically use these autonomously and independently, and so they must be designed with an understanding of how people do this.

Accordingly, both types of methodologies were used in this research in order to develop an in-depth evidence base for digital interventions to enhance adherence to anti-hypertensive medication. An overview of the study design is presented in Figure 2.1



*Figure 2.1.* Research design incorporating qualitative and quantitative methods

In this research, a systematic review was conducted in study 1 to identify the evidence base related to the barriers and facilitators associated with anti-hypertensive adherence. In order to characterise the contemporary digital adherence interventions that are available to patients with hypertension, a content analysis of the behaviour change techniques in smartphone apps for medication adherence was conducted as study 2. Study 3 involved gaining General Practitioners' (GPs') thoughts and perspectives on these types of commercially available apps through a qualitative interview study. Finally, a further

qualitative study was conducted in study 4 to gain an understanding of patients with hypertension's perspectives on using a digital intervention to self-manage their condition.

## **2.4 Study 1 – Identifying the evidence base**

### **2.4.1 Aims and objectives of study 1**

The aims of study 1 were to evaluate the effectiveness of adherence interventions for hypertension on blood pressure control and medication adherence that have been evaluated in RCTs and to explore which specific barriers and facilitators the interventions may have been targeting and how various approaches are associated with the observed effect sizes of these interventions on blood pressure. According to the MRC guidelines (Craig et al., 2008), complex interventions should be developed systematically using the best available evidence. Therefore a systematic review and meta-analysis was conducted in study 1 as a recent and high quality relevant review was not available.

### **2.4.2 Approach to study 1**

The “gold-standard” of evidence synthesis - a Cochrane Review – was published by Nieuwlaat et al. (2014) on interventions to enhance medication adherence. Due to the heterogeneity of interventions and outcomes across a wide range of conditions in the full review, it was not feasible to conduct a meta-analysis as part of the evidence synthesis.

However, all of the included interventions on hypertension had a common outcome of change in blood pressure in addition to the outcome of medication adherence. The homogeneity and continuous nature of blood pressure measurement as a primary outcome provided a common outcome variable with the requisite validity, reliability and sensitivity that is typically absent in adherence behaviour measurement. This rationale has previously been adopted in other quantitative syntheses of adherence intervention studies in Type 2

diabetes (e.g. Vignon Zomahoun et al., 2015). We saw this as an opportunity to conduct quantitative synthesis on the primary outcome of blood pressure change and additional hypertensive specific analysis that was not possible in the previous review conducted by Nieuwlaat et al. (2014).

Secondly, interventions for enhancing adherence to antihypertensives can have multiple components, such as education around the condition and the importance of adherence, skills development, combination pills, provision of practical support and self-monitoring of blood pressure and can be delivered in range of contexts by various healthcare providers. These interventions have had mixed results (e.g. Amado Guirado et al., 2011; Matsumura et al., 2012). The Theoretical Domains Framework (TDF) is an integrative framework which was developed and validated to summarise the range of psychological theory underpinning behaviour change into distinct factors (Cane, O'Connor, & Michie, 2012; Michie et al., 2005). By applying the TDF to adherence interventions in the context of hypertension treatment, it may be possible to explore which theoretical domains modify the effect sizes. To the best of our knowledge, identifying whether the targeting of particular theoretical domains in the interventions is associated with greater effect sizes in adherence interventions in hypertension had not been done previously. Recent studies have attempted to synthesise existing evidence using a similar general approach (e.g. Little, Preece, & Eccles, 2015). Such analyses can be a valuable addition to the literature as it may inform future refinements of intervention designs.

A detailed protocol (Morrissey et al., 2016) of this review has been published in *BMC Systematic Reviews* and can be seen in Appendix I.

## **2.4.3 Procedure**

### **2.4.3.1 Eligibility criteria**

#### 2.4.3.1.1 Types of studies

The systematic review was a condition-specific update to the large review by Nieuwlaat et al. (2014) on interventions to enhance medication adherence which searched for studies until January 2013. This review included RCTs that provide unconfounded tests of interventions expected to enhance adherence. Studies were included regardless of treatment intensity or duration, mode of treatment delivery or medium of treatment.

#### 2.4.3.1.2 Types of participants

Patients who were prescribed medication for hypertension.

#### 2.4.3.1.3 Types of interventions

Interventions of any sort intended to affect adherence with prescribed, self-administered medication for the treatment of hypertension.

#### 2.4.3.1.4 Types of outcome measures

The primary outcome was change in blood pressure (SBP, DBP, or both) at six months compared with baseline readings taken prior to the intervention. The change in BP tended to be reported as a dichotomous (% with positive/negative BP change) or continuous variable (mean change in BP values). The primary outcome was compared between treatment groups, i.e. the difference between groups regarding the change in BP.

The secondary outcome was medication adherence measured by at least one of the following: self-report, pill count, pharmacy refill records, electronic medication monitors (MEMS).

Interventions had to include both outcomes to be included.

#### 2.4.3.1.5 Follow up completion

Regarding follow up completion, studies needed to have at least 80% follow-up during at least six months. The 80% data completion was required for both blood pressure and adherence outcomes.

### **2.4.3.2 Information sources**

#### 2.4.3.2.1 Search methods for identification of studies

We searched *The Cochrane Library* including CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL and Sociological Abstracts on 25 November 2015. This database search was a hypertension specific update on previous searches that were undertaken on: 1 September 1993; 12 December 1993; 1 June 1994; 30 June 1995; 31 July 1998; 15 August 2001; 30 September 2004; 1 February 2007 and 11 January 2013. We searched new publications since 11 December 2012, that is, having a one-month overlap with the previous search. All databases were originally searched from their start date. Ongoing trials were identified by checking trials and protocols published in relevant databases of current ongoing clinical research studies, specifically World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov.

#### 2.4.3.2.2 Search strategy

The search filters for each database can be seen in Appendix II. We also checked articles cited in reviews and original studies of patient adherence in hypertension.

### **2.4.3.3 Data management**

We used a web-based data management system, developed by the Health Information Research Unit at McMaster University to facilitate screening, data extraction, adjudication of disagreements, author review and confirmation of data, production of data tables, and production of data files for future research use. This system has been successfully used in conducting and completing several large, complex systematic reviews.

#### **2.4.3.4 Selection process**

We re-assessed all RCTs on hypertension included in the 2014 update for eligibility to carry over into the current update. Retrieved citations from the updated search entered a first screening stage. Based on the title and abstract, studies moved to the second screening stage if they meet all five eligibility criteria or if there was uncertainty about their eligibility. In the second screening stage, assessment of the full text determined if studies will be included on the review. At both screening stages, two independent review authors (EM and HD) assessed eligibility and an adjudicator (TN) resolved disagreements. We recorded reasons for excluding citations in the second screening stage and reported these in a PRISMA flow chart.

#### **2.4.3.5 Data collection process**

We imported data from the 2014 review into the update database and checked the data for accuracy. Extracted data included items as provided in the tables from the previous review (Nieuwlaat et al., 2014): the ‘Characteristics of included studies’ table (i.e. methods, participants, interventions, outcome, additional notes pertaining to any one of the aforementioned items, detailed assessment of risk of bias), the ‘Adherence and outcome’ table (i.e. intervention, control, effect on adherence outcome, effect on clinical outcome) and risk of bias summary. We extracted the same items for the new included studies. Two review authors (EM and HD) independently extracted all new data and an adjudicator (TN) resolved disagreements. We contacted primary or corresponding authors of all included RCTs to provide any missing data.

The TDF domains that appeared to be targeted by the interventions and within the control groups were identified and coded independently by two reviewers (EM and GM), using a data extraction form designed for the purpose (See Appendix III). We used domains as well as constructs within domains to inform coding decisions within domains, using

construct definitions as described by Cane et al (2012). Each domain was coded every time it appeared in an intervention, so it was possible that the same domain could be coded more than once. The data extraction form was tested on one included study. The coding of each domain was supported by evidence from the text. Inter-rater reliability was calculated prior to resolving discrepancies. Discrepancies were discussed until 100% agreement is achieved.

#### **2.4.3.6 Assessment of risk of bias in included studies**

Two authors (EM and HD) independently used the Cochrane 'Risk of bias' tool described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011) to assess randomisation procedures, bias, allocation, outcome assessors, reporting of findings and losses to follow up.

#### **2.4.3.7 Measures of treatment effect**

For the primary outcome of BP, we reported mean differences between groups and the 95% confidence intervals (95% CI). Where no standard deviations are reported, we will calculate the standard deviations using the methods described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins, 2011).

For the secondary outcome of medication adherence, the heterogeneity of adherence measures meant it was not feasible to pool effects. Instead we conducted a narrative review based on adherence measure.

#### **2.4.3.8 Unit of analysis issues**

In studies where more than one intervention group is contained in one comparator arm we included both interventions (providing they are relevant to the review) and split the number of participants between the two groups accordingly.

#### **2.4.3.9 Assessment of heterogeneity**

We used the  $I^2$  statistic and the  $\text{Chi}^2$  test to assess heterogeneity as described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011).

#### **2.4.3.10 Assessment of reporting bias**

We assessed reporting bias initially by a visual inspection of funnel plots and then with the use of Eggers test as described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011).

#### **2.4.3.11 Data synthesis**

Data was pooled and analysed where appropriate and feasible. We analysed each outcome measure separately, calculated intervention effects and expressed them as mean differences and with 95% confidence intervals for continuous data. We used a random-effects model which was incorporated into the statistical analysis as substantive statistical heterogeneity is identified. In addition, we used subgroup analyses to assess heterogeneity (see below).

The relationship between the number of different domains coded and the effect size of the intervention was explored using Pearson correlations (two-tailed). This analysis was based on similar work by Little et al. (2015). The maximum possible number of different domains coded was 14 (the number of TDF domains). The number of different domains coded in the control group was subtracted from the number of different domains coded in the intervention group. A sensitivity analysis was performed in which the subtraction of control groups was not done, to examine the effect of the subtraction on the result. An analysis was also conducted where domains were weighted according to the frequency of which they were targeted.

##### **2.4.3.11.1 Subgroup analysis**

Six categories of interventions were used in the included studies, including technological interventions, combination pill interventions, service provision interventions, home BP monitoring interventions and interventions targeted at low adherers. We used subgroup

analysis to categorise these interventions and to explore heterogeneity. We also conducted a subgroup analysis on each of the domains within the TDF.

## **2.5 Study 2 – Characterising the technology base**

### **2.5.1 Aims and objectives of study 2**

Study 1 provided evidence that behavioural interventions for medication adherence can be effective in lowering BP. The most widely available digital behavioural intervention for a patient with hypertension is a smartphone app. However there has been little systematic evaluation of the content of most of these apps. Characterising the content of these commercially available apps is helpful in intervention design as it allows to us understand the technology base which we are working with. Content analyses of apps for behaviour change techniques (BCTs) has been done for smoking cessation and weight loss apps, however this had not been done for medication adherence apps. Therefore, the aim of study 2 was to perform a content analysis of all apps for medication adherence across the Apple App Store and Google Play Store for the presence or absence of established BCTs using the BCTTv1 (Michie et al., 2015).

### **2.5.2 Approach to study 2**

As the nature of hypertension is of a typical chronic disease of older adulthood that is typically found in those with multimorbidity (Barnett et al., 2012), we focused on all medication adherence apps for disease management, rather than narrowing down the search to a potentially limited amount of hypertension-specific medication adherence apps. An increasingly common way of analysing the content of apps is to code them using a behaviour change technique (BCT) taxonomy (Michie et al., 2013) or evidence based lists of specific behaviour change techniques or approaches to behavioural interventions. BCTs are defined as the observable, replicable, components of behaviour change interventions.

The most recent version of a BCT taxonomy is the BCTTv1 which includes 93 distinct BCTs within 16 categories with detailed definitions of each.(Michie et al., 2013) This method has been recently used to analyse apps for physical activity (Conroy, Yang, & Maher, 2014; Middelweerd, Mollee, van der Wal, Brug, & Te Velde, 2014; Yang, Maher, & Conroy, 2015) and diet (Direito et al., 2014).

### **2.5.3 Procedure**

#### **2.5.3.1 Search strategy**

The sample of apps was identified through systematic searches of the two major online marketplaces, the Google Play Store and Apple App Store, in February 2015. Search terms were based on Boolean logic and included “AND” combinations for *medication, pill, adherence, compliance, monitor, reminder, tracker, diary, and management*. These searches were continued until no new relevant results were found.

#### **2.5.3.2 Inclusion criteria**

The inclusion criterion was having medication adherence as main content. Exclusion criteria were having content unrelated to medication adherence for disease management; being a tool for an online intervention rather than stand-alone app; being faulty – unable to use (e.g. crashing/freezing/downloading problems); being specific to a particular country; in a language other than English; and being a paid app that is no more than an advertisement free version of the free app.

#### **2.5.3.3 Coding**

All apps which fell into these search categories and fit into the inclusion criteria were downloaded for analysis. The downloaded apps were screened and coded for BCTs using the BCTTv1 in March 2015. Coding was done independently by two authors (EM and TC) who were both certified in BCT taxonomy coding. The content and functionality of each app was examined on a mobile phone or tablet through extensive exploration of the menu

options and observing the functionalities over a 24 hour period. The description of the app in the app store was also taken into account. BCTs were coded with a “0” if absent and a “1” if present. The inter-rater reliability was calculated and any discrepancies were resolved with discussion and involvement of a third reviewer where necessary until consensus was reached.

#### **2.5.3.4 Analysis**

Statistical analysis was conducted in March 2015 using SPSS, version 20. Descriptive statistics were conducted on the frequency of available BCTs. An independent samples t-test was also conducted to compare the number of BCTs present in free and paid apps.

### **2.6 Study 3 – Developing the evidence base**

#### **2.6.1 Aims and objectives of study 3**

As evidenced in study 2, there are a large amount of apps for medication adherence available to a patient with hypertension. A similar content analysis by Kumar et al. (2015), focused on apps for hypertension management, found that as well as containing tools for specifically for medication adherence (e.g. a pill reminder as identified in study 2) these apps typically also contained a BP tracking function through a wireless BP monitor. There is evidence to suggest that home BP monitoring also has established efficacy to improve adherence (Fletcher, Hartmann-Boyce, Hinton, & McManus, 2015; Glynn, Murphy, Smith, Schroeder, & Fahey, 2010; Vervloet et al., 2012).

In Ireland, the majority of hypertension management occurs in general practice. In order to develop an in-depth evidence base, it useful to investigate how general practitioners (GPs) feel about and engage with the growth of these new digital methods of self-management of blood pressure. With this in mind, the aim of this qualitative research was to explore GPs’

perspectives of contemporary self-management digital interventions to support medication adherence and blood pressure control in patients with hypertension.

### **2.6.2 Approach to study 3**

Semi-structured interviews were selected for data collection for several reasons. Interviews tend to be commonly used for exploring understanding and perception type research question (Braun & Clarke, 2006) so were suitable in this case. In addition to this interviews allow the provision of rich and detailed data about individual experiences in particular geographic and socio-economic circumstances from individuals at varying points in their career. This is conducive to generating contextually relevant data that is unbiased by the social processes that are known to influence data collection in the context of a focus group. For example, the potential for ‘socially desirable responding’ by more junior less experienced members of the focus group while in the presence of more senior members may be likely in healthcare focus groups. Finally, from a pragmatic point of view, GPs in Ireland tend to be self-employed in private practice and like many other international contexts have a high and continuously increasing workload. Because of this, the lead author travelled to the GPs’ clinics and met them individually at a convenient time.

An inductive thematic analysis was used as the method of analysis. This flexible method is used for identifying themes and patterns of meaning across a dataset in relation to the research question. In this case, it allowed themes to be developed in a data-driven, “bottom up” way on the basis of what was in the data (Braun & Clarke, 2013). A data-driven approach was suitable for the research question of “What are GPs’ perspectives of contemporary self-management technology to support medication adherence and blood pressure control in patients with hypertension?” as little research has been done on the

topic to date, meaning analysis within a theoretical framework was not warranted. A semantic realist approach was used as a simple, largely unidirectional relationship could be assumed between meaning, experience and language (Widdicombe & Wooffitt, 1995). This allowed motivations, experience, and meanings to be theorised in a straightforward way. The results of thematic analysis tend to be more accessible to an educated wider audience than other qualitative methodologies (Braun & Clarke, 2013). This is particularly suitable for this work which is published in a general practice journal and aimed at clinicians as well as researchers.

### **2.6.3 Procedure**

#### **2.6.3.1 Recruitment**

GPs from the west of Ireland were recruited purposively based on age, gender, years of practice, practice size and practice location (urban/rural). In order to be responsive to, and incorporate findings from the data as they emerged, an iterative approach was used (Ziebland & McPherson, 2006). As is common in qualitative sampling methodology recruitment continued until data saturation was reached and no new themes emerged (Glaser, Strauss, & Strutzel, 1968).

#### **2.6.3.2 Participants**

Ten GPs were interviewed in total. All participants were provided with information and consent forms (see Appendix VII and VIII). Ethical approval for this study was sought and obtained from Galway University Hospitals Clinical Research Ethics Committee.

#### **2.6.3.3 Data Collection**

The interview topic guide was developed by reviewing other qualitative research in the area. This topic guide was then reviewed by the research team and piloted on one GP. This led to the final topic guide (See Appendix IX). When asking GPs about contemporary self-management technologies, the interviewer described a typical hypertension management

smartphone app that would be seen on the global app market. These tend to consist of two parts – the first is a reminder to take medication, the second is home BP monitoring where the patient has a home BP monitor which is connected to the app via Bluetooth. The monitor sends the BP values to the app and produces a graph of BP measurements. The interviews were semi-structured and carried out by one researcher (EM) who travelled to the GPs' clinics. The participants individually consented to the interviews being conducted and recorded and to anonymous quotations being used. Transcription was fully conducted by the research team as it has been argued that transcription helps the interpretive process and should be seen as the first step in the process of data analysis (Bailey, 2008).

### **2.6.3.3 Analysis**

The five stage of thematic analysis (familiarisation, generation of codes, searching for themes, reviewing themes and defining themes) (Braun & Clarke, 2006) were followed. Coding was partially conducted with another researcher (MC) from a different professional background (nursing) to the main investigator (psychology) for inter-coder reliability (Pope, Ziebland, & Mays, 2000). Coding was initially data-driven using an inductive approach to ensure that the data was analysed comprehensively, without trying to fit into a pre-existing model or analytic framework (Braun & Clarke, 2013). In order to heighten reflexivity, all members of the research team (PhD candidate in health psychology, two health psychologists, a GP and a nurse) came together for the active process of identifying potential themes (Richards, 2014). Codes and collated data relating to each code were reviewed with the aim of identifying similarity and overlap. Patterns salient to the research question, “What are GPs’ perspectives of contemporary self-management technology to support medication adherence and blood pressure control in patients with hypertension?” were identified and four candidate themes were generated. These candidate themes were then revised after going back to both the coded data and the whole dataset. This resulted in

two candidate themes being collapsed together, as a better fit of the research question. The three final themes were then written up using an illustrative approach. NVivo (version 11) was used to organise and code the transcripts to facilitate the analysis and comparison of relationships between codes (Pitney & Parker, 2009).

## **2.7 Study 4 – Developing the evidence and technology base**

### **2.7.1 Aims and objectives of study 4**

Study 3 explored GPs views about smartphone apps to manage hypertension. The other key stakeholders in this area are the patients living with hypertension themselves. While it seems that GPs can see the benefit in these types of technology, although it is weighted against some concerns, it remains unclear whether these technologies are feasible, acceptable and usable for the patients (Hallberg, Ranerup, & Kjellgren, 2016). Therefore, it is useful to investigate how patients with living with hypertension feel about and engage with these types of apps. The app that was used, MiBP, was developed from qualitative work with people with hypertension (Glynn et al., 2015). Additionally, it contains both a home BP monitoring function and a reminder device, which may influence both the reflective system through experiential feedback and automatic system through habit formation, as outlined in the CS-SRM. The aim of this study was to explore patients' perspectives on smartphones apps to improve medication adherence and blood pressure control in hypertension.

### **2.7.2 Approach to study 4**

In order to gain insights into the usability and acceptability of these types of apps, focus groups with people with hypertension were engaged in. Focus groups were an appropriate methodology to use for discussion around the usability of the app as they have high ecological validity and facilitate gathering of new knowledge around issues little is known

about (Braun & Clarke, 2013). They are recommended when the research question requires a wide range of views, perspectives, or understandings of a topic (Underhill & Olmsted, 2003). Focus groups can be also experienced as empowering as the sharing of views meaning that people can realise that they are not so isolated in their experience, making them particularly appropriate for populations with chronic illnesses such as hypertension (Braun & Clarke, 2013).

As this study is complementary with the previous study focusing on GPs, a similar inductive thematic analysis was used. Again this allowed themes to be developed in a data-driven, “bottom up” way on the basis of what was in the data (Braun & Clarke, 2013).. A semantic realist approach was also assumed as a simple, largely unidirectional relationship could be assumed between meaning and experience and language (Widdicombe & Wooffitt, 1995).

### **2.7.3 Procedure**

#### **2.7.3.1 Recruitment & Setting**

Croí- the West of Ireland Cardiac Foundation – is a registered charity based in Galway city. Their work is based around improving quality of life for all through prevention and control of cardiovascular disease. Accordingly, they run several preventative and rehabilitation programmes. Participants for focus groups were recruited through Croí, who advertised it through email and social media channels. Advertising material can be seen in Appendix X.

Participants were sampled purposively based on age, sex, length of hypertension diagnosis and anti-hypertensive prescription and experience with technology. In order to be responsive to, and incorporate findings from the data as they emerged, an iterative approach was used (Ziebland & McPherson, 2006). As is common in qualitative sampling

methodology recruitment continued until data saturation was reached and no new themes emerged (Glaser et al., 1968). The focus groups were conducted in Croí House, the charities dedicated heart and stroke centre.

### **2.7.3.2. Participants**

Patients with hypertension who were prescribed at least one anti-hypertensive medication were eligible to take part. All participants were provided with information and consent forms (see Appendix XI and XII) and received a €20 voucher for their participation.

Ethical approval for this study was sought and obtained from Galway University Hospitals Clinical Research Ethics Committee.

### **2.7.3.3 Data Collection**

Eight focus groups with 24 participants were conducted in total. The amount of participants ranged between 3 and 5 per group. Discussion in the focus groups centred on the usability and acceptability of an app to manage hypertension, as participants interacted with the app for the first time during the focus group. The topic guide was developed by reviewing other qualitative research in the area. This topic guide was then reviewed by the research team and piloted on two patients with hypertension. This led to the final topic guide (Appendix XIII). The participants individually consented to the focus groups being conducted and recorded and to anonymous quotations being used.

### **2.7.3.4 The App**

MiBP is a smartphone app for hypertension self-management. It is typical of current hypertension self-management apps in that it consists of two main – the first is a reminder to take medication, the second is home BP monitoring where the patient has a home BP monitor which is connected to the app via Bluetooth. The monitor sends the BP values to the app and produces a graph of BP measurements.

### **2.7.3.5 Analysis**

The five stage of thematic analysis (familiarisation, generation of codes, searching for themes, reviewing themes and defining themes) (Braun & Clarke, 2006) were followed. Coding was partially conducted with another researcher (MC) from a different professional background (nursing) to the main investigator (psychology) for inter-coder reliability (Pope et al., 2000). Coding was initially data-driven using an inductive approach to ensure that the data was analysed comprehensively, without trying to fit into a pre-existing model or analytic framework (Braun & Clarke, 2013). In order to heighten reflexivity, as in study 3, all members of the research team (PhD candidate in health psychology, two health psychologists, a GP and a nurse) came together for the active process of identifying potential themes (Richards, 2014). Codes and collated data relating to each code were reviewed with the aim of identifying similarity and overlap. Patterns salient to the research question, “What are patients with hypertension’s perspectives of smartphone apps that support medication adherence and blood pressure control?” were identified and three candidate themes were generated. These candidate themes were then revised after going back to both the coded data and the whole dataset. The three final themes were then written up using an illustrative approach. NVivo (version 11) was used to organise and code the transcripts to facilitate the analysis and comparison of relationships between codes (Pitney & Parker, 2009).

### **2.8 Ethical considerations**

Ethical considerations in this research were guided by a framework for evaluating the ethics of health research with human participants based on major ethical codes and declarations (Emanuel, Wendler, & Grady, 2000). The seven requirements according to the framework are as follows:

1. Value must be added in terms of improvements in health or knowledge as a result of the research.
2. The research must be scientifically valid by applying rigorous methodological standards.
3. Fair participant selection must guide recruitment based on scientific objectives and consideration of potential risks and benefits in order to avoid disproportionate distribution of either of vulnerable or privileged groups.
4. A favourable risk-benefit ratio in terms of the risks and benefits to participants as well as society must be present.
5. The research must be subject to ethical review by independent persons with the power to approve amend or terminate it.
6. Participation in the research must be informed and voluntary.
7. Respect must be shown to participants by protecting their privacy, having the opportunity to withdraw, and monitoring their well-being,

Although this framework is aimed at clinical research, it is important that all health research (even that which may pose a smaller risk of harm), is approached with the highest standards. Participants were recruited in studies 3 and 4. Ethical approval was sought and obtained for collection in these studies from Galway University Hospitals Clinical Research Ethics Committee. The primary ethical concerns raised by these two studies related to confidentiality and anonymity and informed consent. The following section will outline how we addressed each of these ethical concerns. The consent forms and information sheets for studies 3 and 4 can be seen in Appendices VII, VIII, XI, XII.

### **2.8.1 Confidentiality & anonymity**

As two studies in this research involved qualitative data collection, securely managing the data was of particular importance. The small samples sizes in studies 3 and 4 were a challenge to confidentiality. Both the interviews and focus groups were recorded using digital recording equipment and the data was immediately saved to a password protected computer. Participants were pseudonymised during transcription, and these transcripts and questionnaires were stored in a secured location. Any other potentially identifying information was not reported.

### **2.8.2 Informed consent**

Informed consent is the cornerstone of the ethical conduct and regulation of research (Bhutta, 2004). The purpose of the procedures for obtaining informed consent in this research was to ensure that the research was in line with the individuals' values and it was truly the decision of the individual to take part in the research (World Medical Association, 2001).

As healthcare providers and a population with a chronic condition, members of the target populations for this research may have been contacted and recruited for numerous studies. This may have affected the willingness of GPs and patients with hypertension to take part in the research in a negative or positive manner. In cases where the research was based in a single setting, as in study 3, or participants were recruited through Croí, as in study 4, the importance of informed and voluntary consent, and adequate time to make a decision, were central to facilitate potential participants to choose, independently, to take part in research which was of interest to them (Hynes, 2015).

## **2.9 Summary of the chapter**

This chapter provided an overview of the study design and details of the methodological approach of each study. The aim of the four studies described in this chapter was to develop an evidence base for a digital intervention to enhance medication adherence to anti-hypertensive medications. A systematic review and meta-analysis, content analysis study and two thematic analysis studies were conducted to address this aim. The main ethical considerations related to confidentiality and anonymity, informed consent and fair participant selection. Measures to address these concerns included secure storage of data and clear consent procedures.

### **3. Study 1: Effectiveness and content analysis of interventions to enhance medication adherence and blood pressure control in hypertension: A systematic review and meta-analysis.**

Morrissey, E.C.<sup>1</sup>, Durand, H.<sup>1</sup>, Nieuwlaat R.<sup>2</sup>, Navarro, T.<sup>2</sup>, Haynes, R.B.<sup>2</sup>, Walsh, J.C.<sup>1</sup>  
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#### **Abstract**

**Objective.** The objective of this systematic review is to evaluate the effectiveness of medication adherence interventions on blood pressure control in hypertensive patients. In addition we aim to explore what barriers and facilitators in the interventions may have been targeted and how these might be related to the effect size on blood pressure (BP).

**Design.** This review is a hypertension-specific update to the previous Cochrane Review by Nieuwlaat et al. (2014) on interventions to enhance medication adherence. A systematic literature search was carried out and two authors independently screened titles and abstracts for their eligibility for inclusion and independently extracted data from the selected studies and assessed the methodological quality using the Cochrane Collaboration Risk of Bias Tool. A meta-analysis was conducted and additionally, theoretical factors in interventions were identified using the Theoretical Domains Framework.

**Results.** The meta-analysis found a modest main effect of adherence interventions on SBP (MD -2.71mmHg, 95% CI -4.17 to -1.26) and DBP (MD -1.25 mmHg, 95% CI -1.72 to -0.79). However there was substantial significant heterogeneity across both outcomes. A narrative review on adherence outcomes was conducted. In terms of the theoretical analysis, the relationship between the total number of times the domains were coded

within an intervention and change of SBP ( $r = -0.234, p = .335$ ) and DBP was not significant ( $r = -0.080, p = .732$ ). Similarly, the relationship between the total number of times *different* domains were coded within an intervention and change of SBP ( $r = 0.080, p = .746$ ) and DBP was not significant ( $r = -0.188, p = .415$ ).

**Discussion.** This review and meta-analysis of interventions documented significant but modest post-intervention improvements in BP outcomes among hypertensive patients. However this is a tentative finding as substantial heterogeneity and potential biases were present. One of the greatest challenges of this review was assessing risk of bias, extracting sufficient data to calculate effect size and coding interventions with the amount of information provided in papers. It is imperative that future adherence research comprehensively reports methodology.

### **Trial registration**

This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42016033358) on 26<sup>th</sup> January 2016.

### **Keywords**

Hypertension, medication adherence, blood pressure, compliance, systematic review, meta-analysis

### **3.1 Background**

Hypertension is a chronic condition in which the blood vessels have persistently raised pressure. There is substantial evidence that hypertension is a major modifiable risk factor for cardiovascular disease events (e.g. stroke, heart failure, myocardial infarction and unstable angina) and therefore the treatment of this condition is a key focus of primary

and secondary prevention of cardiovascular disease in both economically developed and developing countries (Amici et al., 2009; Kearney et al., 2005; Pini et al., 2008). The World Health Organisation (WHO) estimates that hypertension affects one billion people worldwide and is therefore a major global health challenge (Alwan, 2011).

The pharmacological treatment of hypertension has led to substantial benefits in the prevention of morbidity and mortality from cardiovascular disease (Wright & Musini, 2009). A Cochrane review of all trials of antihypertensive medications by Musini, Tejani, Bassett, and Wright (2009) in people with hypertension aged 60 years and over and found that these treatments reduced morbidity and mortality. However, despite their established efficacy, there is a significant problem of non-adherence to these treatments in those diagnosed with hypertension; therefore the effectiveness of current medications is sub-optimal.

The WHO defines adherence to long-term therapy as ‘the extent to which a persons behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider’ (Sabaté, 2003).

High adherence which is often defined as medication possession ratios of 80 % to 100% to hypertensive medications is associated with higher odds of blood pressure control compared with those with medium or low levels of adherence (Bramley et al., 2006).

Evidence from several studies suggests that as many as 50% to 80% of patients prescribed pharmacological antihypertensive therapy have low adherence to their treatment regimen (Elliott, 2008). Vrijens et al. (2008) used medication event monitor system (MEMS) data to measure adherence to antihypertensive medications and found that about half of all patients prescribed the medications stopped taking them within one year of the initial prescription. They also found that on any one day, 10% of patients omitted their scheduled dose of medication. Such small deviations can be clinically important as (Bailey et al.,

2010) estimated that increasing adherence to antihypertensives by just one tablet per week could reduce the hazard of stroke by 8–9 % and of death by 7 %. According to the WHO, this lack of adherence to antihypertensive medication is the most important cause of failure to achieve BP control (Sabaté, 2003).

Interventions for enhancing adherence to antihypertensives can have multiple components, such as education around the condition and the importance of adherence, skills development, combination pills, provision of practical support and self-monitoring of blood pressure and can be delivered in range of contexts by various healthcare providers. These interventions have had mixed results (e.g. Amado Guirado et al., 2011; Matsumura et al., 2012). Recently Conn et al. (2015) conducted a meta-analysis of both randomized and non-randomized studies that targeted anti-hypertensive medication adherence improvement. The results found that 112 intervention vs control group comparisons had a standardised mean difference effect size of 0.30 (SD 0.08,  $p < 0.001$ ) on measures of adherence. The analysis also revealed that there was considerable heterogeneity across studies ( $I^2 = 87\%$ ), which can be explained by heterogeneity in the methodologies employed and in particular the samples studied, the research designs and measures used to assess adherence.

Because interventions for improving adherence in hypertension are typically multi-factorial, it can be difficult to ascertain which factors can explain the efficacy of the intervention. Theories from the behavioural sciences can be used to gain an understanding of the effects of the behaviour change intervention. It is often the case that papers do not report the explicit use of such theory despite interventions almost certainly involving at least an implicit idea of what factors are likely to instigate change (Little et al., 2015). This means that even if an intervention is successful, it is difficult to understand the behaviour

change processes responsible and therefore to inform future intervention design, refinement and application.

One approach which may shed light on intervention components that are likely to bring about improvements in adherence involves retrospectively identifying which domains efficacious adherence interventions report targeting. These domains can be mapped onto pre-existing theoretical factors that are known to be determinants of behaviour and behaviour change. In order to capture the potential range of possible targeted factors, a sufficiently broad framework of theoretical factors is required. The Theoretical Domains Framework (TDF) is an integrative framework which was developed and validated to summarise the range of psychological theory underpinning behaviour change into distinct factors (Cane et al., 2012; Michie et al., 2005). By applying the TDF to adherence interventions in the context of hypertension treatment, it may be possible to explore which theoretical domains modify the effect sizes of interventions on blood pressure or the predictors of adherence as has been conducted in a number of recent studies (e.g. Cahir, Guinan, Dombrowski, Sharp, & Bennett, 2015; Little et al., 2015).

There are two principle justifications for this review. Firstly, it is a hypertension-specific update to the previous Cochrane review by Nieuwlaat et al. (2014) on interventions to enhance medication adherence that were evaluated using randomised controlled trial research (RCT) designs. Due to the heterogeneity of interventions and outcomes across a wide range of conditions in the full review, it was not feasible to conduct a meta-analysis as part of the evidence synthesis. As this study is focusing specifically on hypertension, it is anticipated that many of the included interventions will have a common outcome of change in blood pressure in addition to the outcome of medication adherence. This will allow quantitative synthesis on the primary outcome of blood pressure change and additional hypertensive specific analysis that was not possible in the previous review.

Secondly, to the best of our knowledge, identifying whether the targeting of particular theoretical domains in the interventions is associated with greater effect sizes in adherence interventions in hypertension has not been done previously. Recent studies have attempted to synthesise existing evidence using a similar general approach (e.g. Little et al., 2015). Such analyses can be a valuable addition to the literature as it may inform future refinements of intervention designs.

### **3.1.1 Objectives**

The objective of this review is to evaluate the effectiveness of adherence interventions for hypertension on blood pressure control and medication adherence that have been evaluated in RCTs and to explore which specific barriers and facilitators the interventions may have been targeting and how this tailored approach might be related to the effect size of these interventions on blood pressure.

## **3.2 Methods**

This systematic review and meta-analysis has been conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009) and is registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42016033358). The protocol has been published (Morrissey et al., 2016).

### **3.2.1 Eligibility Criteria**

#### **3.2.1.1 Types of studies**

The systematic review is a condition-specific update to the large review by Nieuwlaat et al. (2014) on interventions to enhance medication adherence which searched for studies until January 2013. This review included randomised controlled trials (RCTs) that provide

unconfounded tests of interventions expected to enhance adherence. Studies were included regardless of treatment intensity or duration, mode of treatment delivery or medium of treatment.

### **3.2.1.2 Types of participants**

Patients who were prescribed medication for hypertension.

### **3.2.1.3 Types of interventions**

Interventions of any sort intended to affect adherence with prescribed, self-administered medication for the treatment of hypertension.

### **3.2.1.4 Types of outcome measures**

The primary outcome was the change in blood pressure (SBP, DBP, or both) at six months compared with baseline readings taken prior to the intervention. The change in BP was reported as a dichotomous (% with positive/negative BP change) or continuous variable (mean change in systolic and diastolic BP values). The primary outcome was compared between treatment groups, i.e. the difference between groups regarding the change in BP.

The secondary outcome was medication adherence measured by at least one of the following: self-report, pill count, pharmacy refill records, electronic medication monitors (MEMS).

Interventions had to include both outcomes to be included.

### **3.2.1.5 Follow up completion**

Studies needed to have at least 80% follow-up completion after at least six months. The 80% data completion was required for both blood pressure and adherence outcomes.

### **3.2.2 Information sources**

#### **3.2.2.1 Search methods for identification of studies**

We searched *The Cochrane Library* including CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL and Sociological Abstracts on the 25 November 2015. This database search was a hypertension specific update on previous searches that were undertaken on: 1 September 1993; 12 December 1993; 1 June 1994; 30 June 1995; 31 July 1998; 15 August 2001; 30 September 2004; 1 February 2007 and 11 January 2013. We searched new publications since 11 December 2012, that is, having a one-month overlap with the previous search. All databases were originally searched from their start date. Ongoing trials were identified by checking trials and protocols published in relevant databases of current ongoing clinical research studies, specifically World Health Organisation International Clinical Trials Registry Platform and ClinicalTrials.gov.

#### **3.2.2.2 Search strategy**

The search filters for each database can be seen in Appendix II. We checked articles cited in reviews and original studies of patient adherence in hypertension. We contacted authors of included RCTs to identify additional studies.

### **3.2.3 Study Records**

#### **3.2.3.1 Data management**

We used a web-based data management system, developed by the Health Information Research Unit at McMaster University to facilitate screening, data extraction, adjudication of disagreements, author review and confirmation of data, production of data tables, and production of data files for future research use. This system has been successfully used in conducting and completing several large, complex systematic reviews (e.g. Haynes & Wilczynski, 2010; Nieuwlaat et al., 2014).

### **3.2.3.2 Selection process**

We re-assessed all RCTs on hypertension included in the 2014 update for eligibility to carry over into the current update. Retrieved citations from the updated search entered a first screening stage. Based on the title and abstract, studies moved to the second screening stage if they met all five eligibility criteria or if there was uncertainty about their eligibility. In the second screening stage, assessment of the full text determined if studies were included on the review. At both screening stages, two independent review authors (EM and HD) assessed eligibility and an adjudicator (TN) resolved disagreements. Cohen's Kappa ( $\kappa$ ) was run to determine the extent of agreement between two independent raters. According to the guidelines from Landis and Koch (1977) there was moderate strength of agreement between the reviewers,  $\kappa = 0.52$ . We recorded reasons for excluding citations in the second screening stage. These can be seen in the PRISMA flow chart (Figure 3.1).

### **3.2.4 Data Collection and Analysis**

#### **3.2.4.1 Data Collection Process**

We imported data from the 2014 review into the update database and checked the data for accuracy. Extracted data included items as provided in the tables from the previous review (Nieuwlaat et al., 2014): the 'Characteristics of included studies' table (i.e. methods, participants, interventions, outcome, additional notes pertaining to any one of the aforementioned items, detailed assessment of risk of bias), the 'Adherence and outcome' table (i.e. intervention, control, effect on adherence outcome, effect on clinical outcome) and risk of bias summary. We extracted the same items for the new included studies. The data extraction form can be seen in Appendix III. In addition, we extracted items from the Cochrane 'Risk of bias' tool for all included studies from the previous and current update (Higgins et al., 2011). Two review authors (EM and HD) independently extracted all new data and an adjudicator (TN) resolved disagreements. We contacted primary or

corresponding authors of all included RCTs to confirm extracted data and provide missing data. We reported intervention effects in individual RCTs for all outcomes for a) adherence and b) clinical outcomes.

The TDF domains that appeared to be targeted by the interventions and within the control groups were identified and coded independently by two reviewers (EM and GM), using a data extraction form designed for the purpose. This can be seen in Appendix IV. We used domains as well as constructs within domains to inform coding decisions within domains, using construct definitions as described by Cane et al (2012). Each domain was coded every time it appeared in an intervention, so it was possible that the same domain could be coded more than once. The data extraction form was tested on one included study. The coding of each domain was supported by evidence from the text. Inter-rater reliability was calculated prior to resolving discrepancies (Cohen's kappa:  $\kappa = 0.676$ , substantial agreement (Landis & Koch, 1977)). Discrepancies were discussed until 100% agreement was achieved. A correlational analysis was conducted between the amount of times any of the domains were coded with the change in SBP and DBP. Similarly, a correlational analysis was conducted between the amount of times different domains were coded and the change in SBP and DBP. A significant result would mean that with an increasing frequency of any domain coding, the BP decreased by a significant amount.

### **3.3 Results**

#### **3.3.1 Description of Studies**

##### **3.3.1.1 Results of the Search**

The new search identified 1105 citations of which we assessed 88 in full text. Of these, we included 9, based on a full text review in the second screening phase. The PRISMA flowchart shows the results for the selection of papers and is provided in Figure 3.1.

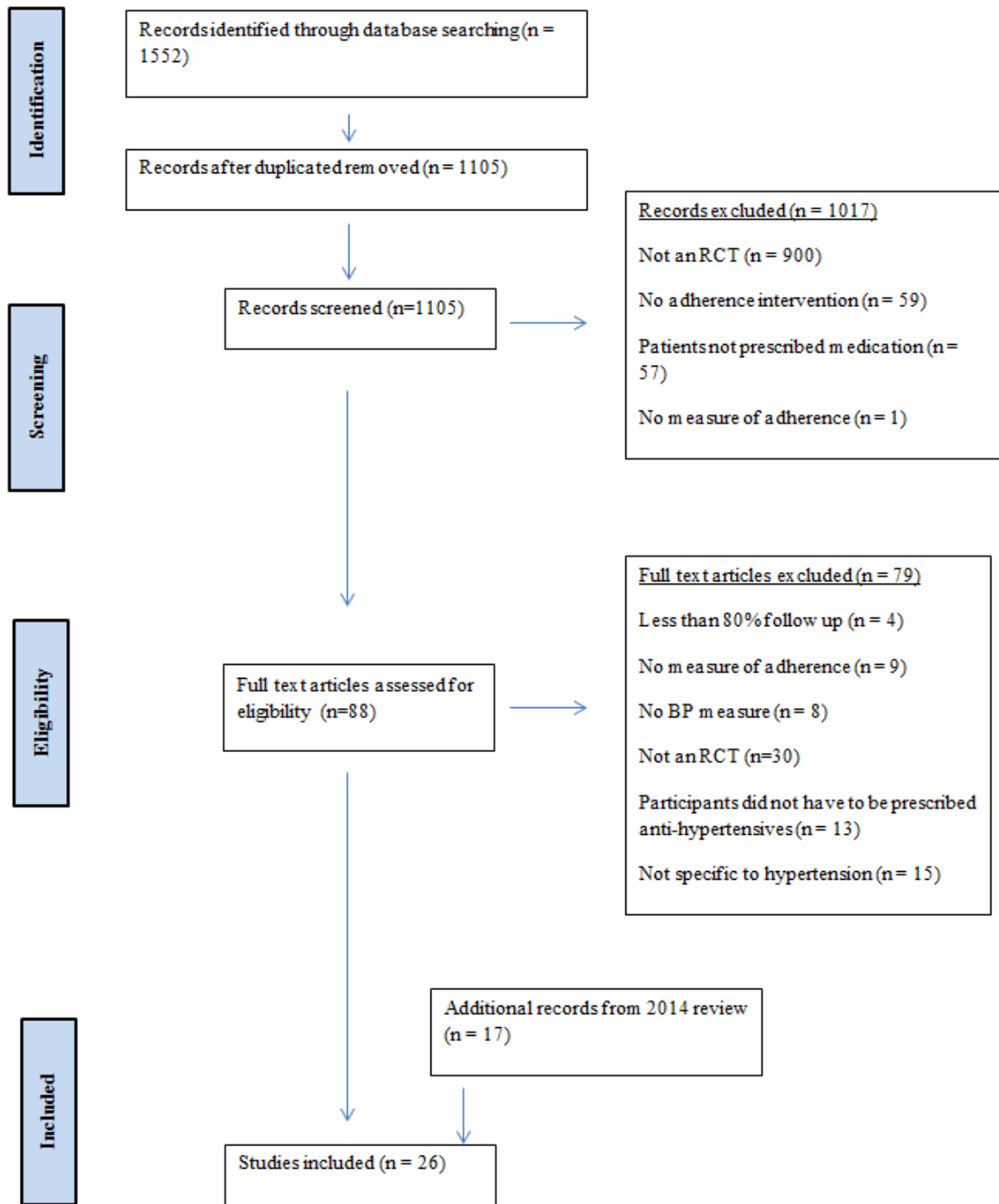


Figure 3.1. PRISMA flowchart of included studies

### **3.3.1.2 Included Studies**

The previous update included 17 RCTs on hypertension, all of which were carried over into the current update. Therefore, we included a total of 26 RCTs in the current update. The overall number of participants was 8967 (4731 intervention and 4236 controls).

Key features of all 26 RCTs are summarised in Appendix V ‘Characteristics of included studies’ and Table 3.1 ‘Adherence and clinical outcomes’.

Of these, 24 were from high-income countries (9 from USA) and one was from an upper middle income country (World Bank classification, <http://data.worldbank.org/about/country-classifications/country-and-lending-groups>). Dusing, Handrock, Klebs, Tousset, and Vrijens (2009) did not provide a study location but the authors were based in Germany.

### **3.3.1.3 Comparisons**

Twenty one trials compared interventions to usual care, two to education only, two to behavioural placebo and one to wait-list control.

### **3.3.1.4 Excluded Studies**

Of the 1105 unique citations detected, we excluded 1017 studies during the title and abstract screen (Figure 3.1). We excluded an additional 79 studies during the full-text screen (Figure 3.1).

### **3.3.2 Assessment of Risk of Bias in Included Studies**

Although all included studies were RCTs, their risk of bias varied considerably because of study design or conduct. Review author agreement was moderate for determining risk of bias for random sequence generation ( $\kappa = 0.50$ , 95% CI -0.02 to 1.02) and fair for the risk of bias for allocation concealment ( $\kappa = 0.33$ , 95% CI -0.41 to 1.07). A third adjudicator resolved differences in the duplicate independent assessments.

### **3.3.2.1 Allocation (Selection Bias)**

Twelve of the studies described the process of allocating participants between study groups randomly, providing details about the method of randomization employed.

Fourteen of the studies were deemed to have an unclear risk of selection bias as insufficient detail about the generation of the random sequence was provided.

Twelve of the studies were judged as having low risk of bias as the method of allocation concealment was well described. Thirteen studies were judged as having an unclear risk of bias, as the method of allocation concealment either was not described or not described in sufficient detail to allow a definite judgment. One study had a high risk of selection bias as the participants or investigators might have foreseen assignment to the study groups.

### **3.3.2.2 Blinding (Performance Bias and Detection Bias)**

Seventeen of the trials included in this review were at high risk of performance bias in the adherence measure owing to the subjective nature of these measures. Seven were judged to have unclear risk of bias and just two were considered low risk. In terms of the patient outcome, 13 studies did not have sufficient information to make a definite judgement.

Eight had a low risk of bias and five were considered to be high risk.

Most studies successfully blinded outcome assessors to the group allocation of participants and were judged to have low risk of bias. Eight did not provide enough information to make a judgement and 4 had a high risk of bias.

### **3.3.2.3 Incomplete Outcome Data (Attrition Bias)**

All studies provided some details of study attrition. Half were at a low risk of bias, with good completion rates. Thirteen trials were considered to have an unclear risk for attrition bias.

#### **3.3.2.4 Selective Reporting (Reporting Bias)**

Most trials had an unclear risk of reporting bias, as study protocols were not available.

Seven studies were at a low risk as, based on the information provided by the study protocols; it was unlikely that there was selective reporting of the primary and secondary outcomes. Two trials were considered high risk. Satisfaction with and willingness to pay for the service were outcomes specified in the original protocol but were not reported in the Stewart et al. (2014) paper. Similarly, cost-effectiveness is mentioned in the protocol for the Svarstad et al. (2013) paper but is not reported on.

#### **3.3.2.5 Other Potential Sources of Bias**

Eleven trials were deemed to have an uncertain risk for other biases such as baseline differences, inappropriate influence of the study sponsor, and early stopping for benefit. Nine were judged to have a low risk of bias and six had a high risk.

A summary of the risk of bias in all 26 studies is shown in Figures 3.2 and 3.3.

Detailed information on risk of bias for all 26 RCTs is reported in Appendix VI.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Other bias	Blinding of outcome assessment (detection bias): Patient Outcome	Blinding of outcome assessment (detection bias): Adherence Measure	Blinding of participants and personnel (performance bias): Patient Outcome	Blinding of participants and personnel (performance bias): Adherence measure	Incomplete outcome data (attrition bias): Patient Outcome	Incomplete outcome data (attrition bias): Adherence Measure
Amado 2011	?	?	?	?	?	?	?	?	+	+
Baird 1984	?	?	?	?	?	?	?	?	-	?
Becker 1986	?	?	?	+	+	?	+	-	?	?
Dusing 2009	?	?	?	?	?	+	+	-	?	?
Friedberg 2014	+	+	+	+	+	+	-	+	+	+
Friedman 1996	?	?	?	?	?	?	+	-	?	?
Girvin 1999	?	?	?	?	+	-	+	-	?	?
Greer 2014	?	-	?	?	-	-	-	-	+	+
Haynes 1976	+	+	?	-	+	+	?	+	+	+
Hosseininasab 2014	+	?	+	?	+	+	?	-	?	?
Johnson 1978	?	?	?	?	?	?	?	-	+	+
Ma 2013	?	+	?	-	-	+	?	?	?	?
Margolius 2012	?	+	?	-	+	+	+	-	+	+
Marques Contreras 2005	+	+	+	+	?	+	?	?	?	?
Marquez Contreras 2006	+	+	?	?	?	?	+	?	?	?
Matsumura 2012	+	+	?	-	?	?	-	?	+	+
Morgado 2011	+	+	+	+	-	+	?	-	+	+
Ogedegbe 2012	+	?	+	+	+	+	-	?	+	+
Ogedegbe 2015	?	?	+	?	+	+	?	-	+	?
Rudd 2004	+	?	?	+	?	+	?	-	+	+
Sackett 1975	?	+	?	+	+	+	?	-	?	?
Schroeder 2005	+	+	?	-	?	+	?	-	?	?
Stewart 2014	?	?	-	+	-	-	+	-	?	?
Svarstad 2013	+	+	-	+	+	+	+	-	+	+
Tinsel 2013	?	+	+	-	+	-	+	-	?	+
Wong 2013	+	?	?	?	+	+	?	-	+	+

Figure 3.2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

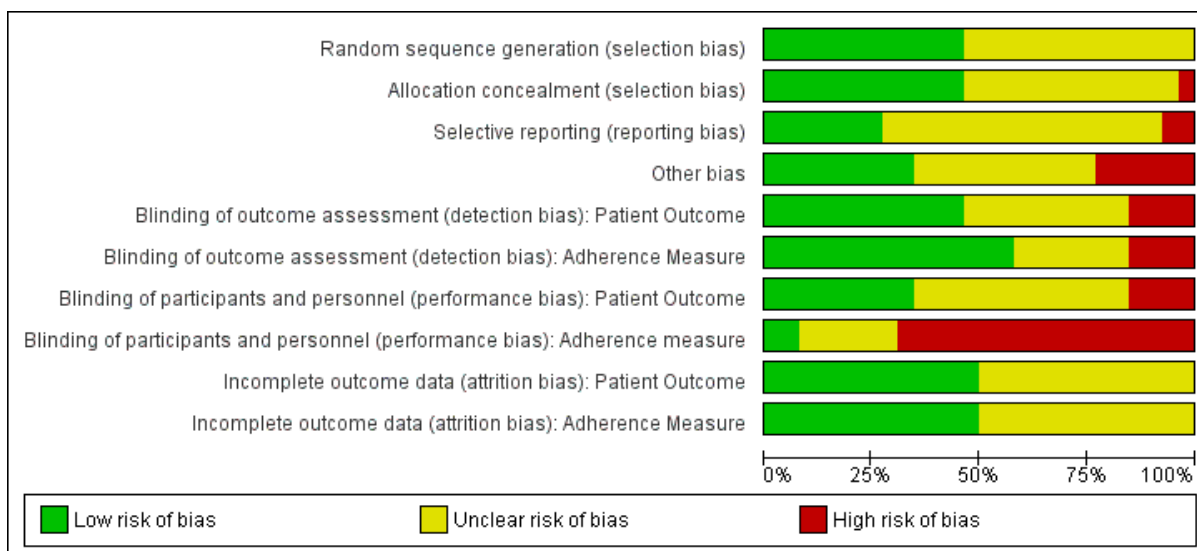


Figure 3.3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

### 3.3.3 Effects of Interventions

This review aimed to critically summarise the evidence about the effectiveness of interventions to enhance medication adherence in patients with hypertension. Detailed information regarding treatment and outcome for all 26 RCTs is provided in Table 3.1. We completed a meta-analysis for the patient outcomes for the follow up time period at up to 6 months. Seven of the included trials did not provide enough statistical information to calculate mean difference and so were not included in the meta-analysis.

When we found heterogeneity, we investigated subgroups based on *a priori* assumptions outlined in the study protocol

#### 3.3.3.1 Overall Effects

A summary of the effects on BP outcomes can be seen in Table 3.1.

Table 3.1

*Adherence and clinical outcomes*

	Country	Participants	Eligibility criteria	Effect on adherence	Effect on clinical outcome
Amado 2011	Spain	996 patients; mean age 63	18-80 years; hypertension; visiting the clinic for at least 6 months for long term follow up; control of hypertension using anti- hypertensive drug therapy	<u>Self-report</u>  Haynes-Sackett: yes  MMAS-8: no  Pill count: no	SBP: no  DBP: no  BP control: no  BMI: no  No of antihypertensive drugs taken: no
Baird 1984	Canada	389 patients; mean age 53	Mild-moderate hypertension; adequately controlled with a regimen of metoprolol 200mg daily or propranolol 160 mg daily	Pill count: yes	SBP: no  DBP: no

Becker 1986	USA	180 patients; <20% employed, primarily middle aged black women	20-80 years; on medication for previously diagnosed hypertension; have demonstrated poor blood pressure control on at least 1 visit in the preceding 2 years	<u>Self-report</u>  Patient interview: no  Pill count: no	DBP: no  BP control: no
Dusing 2009	Not provided	206 patients; mean age 51	>18 years; newly diagnosed with hypertension or not treated for 1 year	MEMS: no	SBP: no  DBP: no  BP control: no
Friedberg 2014	USA	553 patients; mean age 66	Hypertension, antihypertensive drug therapy for >6 months and uncontrolled BP during screening.	<u>Self-report</u>  MMAS-8: no	SBP: no  BP control: yes for the SMI group

Friedman 1996	USA	267 patients; mean age 76	>60 years; under care of physician for hypertension; prescribed hypertensive medication; systolic BP > 160 mm Hg, diastolic BP > 90 mm Hg.	Pill count: yes	SBP: yes DBP: yes
Girvin 1999	Northern Ireland	27 patients; mean age 62	History of mild hypertension; diastolic BP between 90 - 110 mm Hg	Pill count: no MEMS: yes	SBP: no DBP: no
Greer 2014	USA	60 African American women; mean age 58	>18 years, self-identification as African American, diagnoses of primary hypertension and resting SBO greater than 140mmHg or a DBP greater then 90 mmHg	<u>Self-report</u> HBCHBPT: no	DBP: no
Haynes 1976	Canada	38 steelworkers	High blood pressure; treated with antihypertensive medication; non-	Pill count: yes	DBP: no

			adherent with prescribed therapy; not at goal pressure by 6th month of treatment		
Hosseininasab 2014	Iran	194 patients; mean age 59	>18 years, new cases with a diagnosis of mild to moderate hypertension or already on antihypertensive therapy but not controlled	Pill count: yes	SBP: no DBP: no
Johnson 1978	Canada	140 patients; mean age 53	35-65 years; on hypertensive medication for at least one year; elevated diastolic BP	<u>Self-report</u> Patient interview: no  Pill count: no	DBP: no
Ma 2013	China	120 patients; mean age 59	>18 years; diagnosed with essential hypertension by a cardiovascular physician; taking at least one antihypertensive	TAQPH: yes	SBP: yes DBP: yes

			medication		
Margolius 2012	USA	237 patients; mean age 60	>30 years, BP of at least 145 systolic or 90 diastolic	<u>Self-report</u> MMAS-8: no	SBP: no DBP: no Change in number of primary care visits: no
Marquez-Contreras 2005	Spain	636 patients; mean age 61	18-80 years; newly diagnosed or uncontrolled hypertension	Pill count: yes	BP control: yes SBP: yes DBP: yes
Marquez-Contreras 2006	Spain	250 patients; mean age 59	18-80 years; newly diagnosed or uncontrolled hypertension	MEMS: yes	SBP: no DBP: yes
Matsumura 2012	Japan	207 patients; mean age 64	>20 years; hypertension; treatable with ARBs and diuretics	Pill count: no	SBP: no DBP: no BP control: no

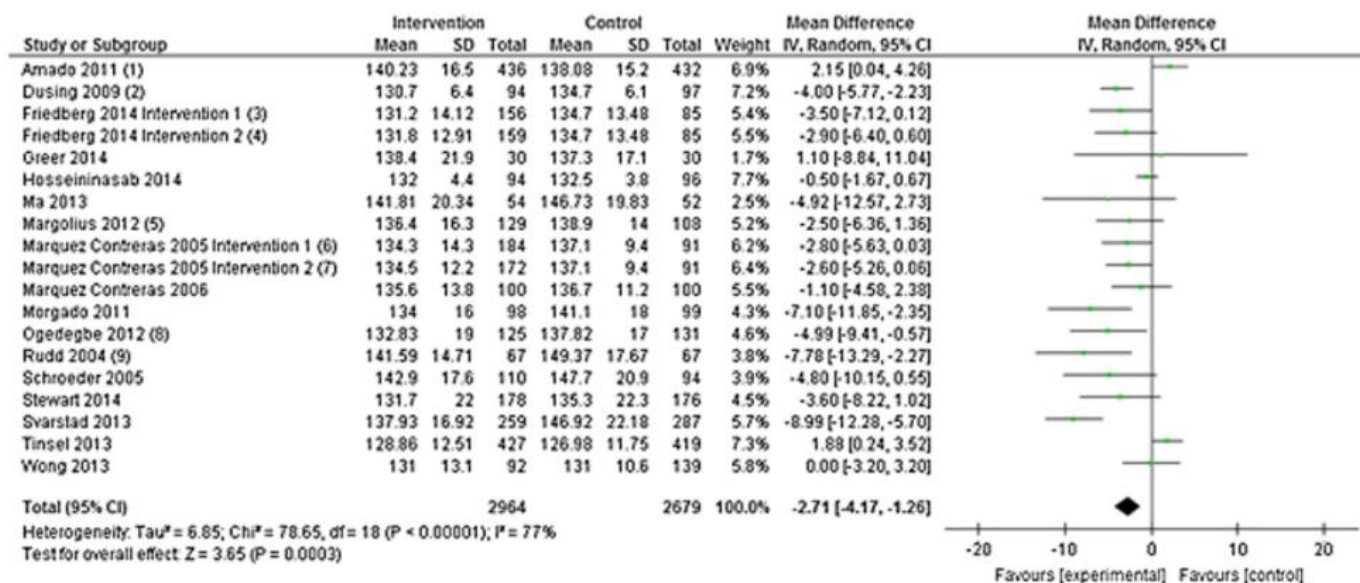
Morgado 2011	Portugal	197 patients; mean age 59	>18 years; hypertension; control of hypertension using anti- hypertensive drug therapy	MMAS-8: yes	BP control: yes  SBP: yes  DBP: yes  Patient knowledge of target BP values: yes
Ogedegbe 2012	USA	256 patients; mean age 58	Hypertension; control of hypertension using anti-hypertensive drug therapy; African American	MEMS: yes	SBP: no  DBP: no
Ogedegbe 2015	USA	1039 African American patients; mean age 57	Self-identification as African American, uncontrolled hypertension	MMAS-8: no	BP control: no
Rudd 2004	USA	150 patients; mean age 60	Hypertension; BP > 150 mmHg systolic, 95 mmHg diastolic, or both	MEMS: yes	SBP: yes  DBP: yes
Sackett 1975	Canada	230	Hypertension; no secondary	Pill count: no	BP control: no

		steelworkers	hypertension; no other meds; control of hypertension using anti-hypertensive drug therapy		
Schroeder 2005	UK	245 patients; mean age 68	Hypertension; no secondary hypertension; in control of meds	MEMS: no	SBP: no DBP: no
Stewart 2014	Australia	395 patients; mean age 67	>18 years, diagnosis of primary hypertension, using or having had used at least one anti-hypertensive medication in the previous 6 months	MMAS-8: no TABS: no	SBP: yes DBP: no
Svarstad 2013	USA	576 African American patients; mean age 53	>18 years, self-identified as African American, have one or more BP prescriptions, mean BP of 140/90 mmHg or more	Refill records: yes	SBP: yes DBP: yes BP control: no

Tinsel 2014	Germany	1120 patients; mean age 64	>18 years; repeated prescription of antihypertensive medication	Self-report  MARS-D: no	SBP: yes  DBP: no  Cardiovascular risk: no
Wong 2013	China	274 patients; mean age 62	>18 years, taking at least one anti- hypertensive ages, evaluated as having suboptimal compliance to antihypertensive medication as assessed by the Morisky self- reported adherence questionnaire.	MMAS-8: no	SBP: no  DBP: no  BP control: no

### 3.3.3.2 Meta-Analysis

**SBP.** A meta-analysis of the mean difference between the groups at follow up between adherence and control interventions demonstrated a significant improvement ( $p < 0.001$ ) in SBP at 6 month follow up of -2.71 mmHg (95% CI, -4.17 to -1.26 mmHg),  $I^2 = 77\%$ . The forest plot can be seen in Figure 3.4.

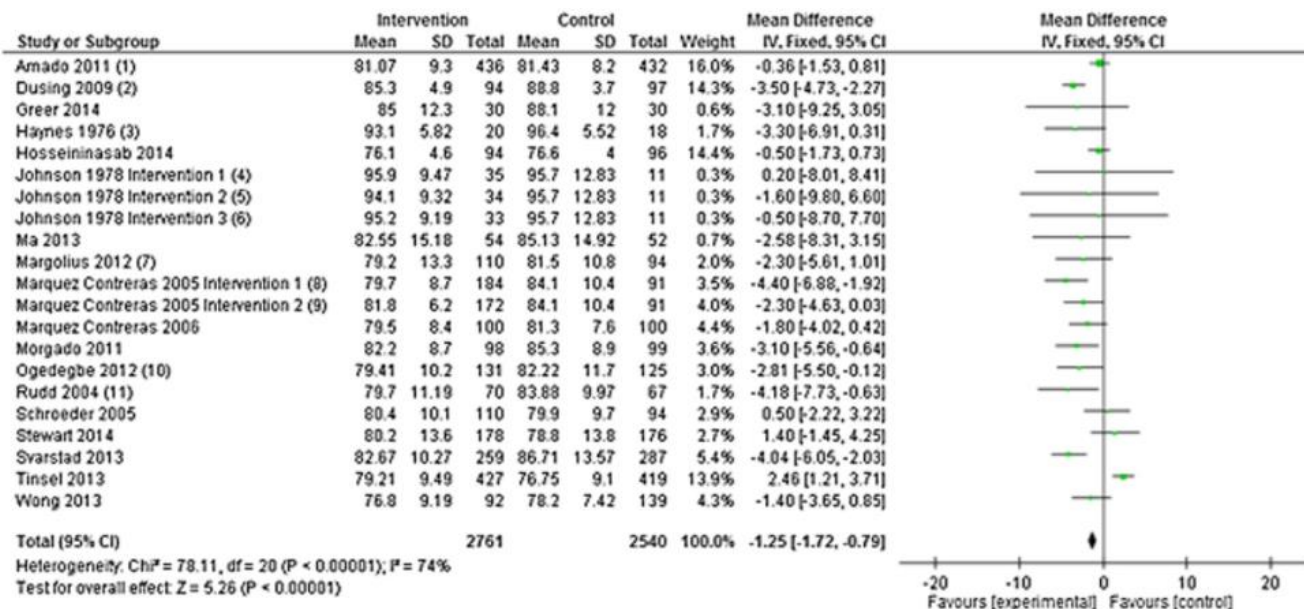


#### Footnotes

- (1) Follow up SD provided by author
- (2) SD at follow up not provided. Baseline SD used.
- (3) Control group split in two due to two comparators as recommended in section 16.5.4. of the Cochrane Handbook. SD calculated using CI provided.
- (4) Control group split in two due to two comparators as recommended in section 16.5.4. of the Cochrane Handbook. SD calculated using CI provided.
- (5) Follow up SD not provided. Baseline SD used.
- (6) Control group split in two due to two comparators as recommended in section 16.5.4. of the Cochrane Handbook
- (7) Control group split in two due to two comparators as recommended in section 16.5.4. of the Cochrane Handbook
- (8) Follow up SD not provided. Baseline SD used.
- (9) Mean, SD and n provided by author

Figure 3.4. Meta-analysis of effect of interventions on SBP

**DBP.** A meta-analysis of the mean difference between the groups at follow up between adherence and control interventions demonstrated a significant improvement ( $p < 0.001$ ) in DBP at 6 month follow up of -1.25 mmHg (95% CI -1.72 to -0.79 mmHg),  $I^2 = 74\%$ . The forest plot can be seen in Figure 3.5.



**Footnotes**

- (1) Follow up SD provided by author
- (2) Follow up SD not provided. Baseline SD used.
- (3) SD calculated using SE provided.
- (4) Control group split in three due to three comparators as recommended in section 16.5.4. of the Cochrane Handbook. SD calculated using SE provided.
- (5) Control group split in three due to three comparators as recommended in section 16.5.4. of the Cochrane Handbook. SD calculated using SE provided.
- (6) Control group split in three due to three comparators as recommended in section 16.5.4. of the Cochrane Handbook. SD calculated using SE provided.
- (7) Follow up SD not provided. Baseline SD used.
- (8) Control group split in two due to two comparators as recommended in section 16.5.4. of the Cochrane Handbook.
- (9) Control group split in two due to two comparators as recommended in section 16.5.4. of the Cochrane Handbook.
- (10) Follow up SD not provided. Baseline SD used.
- (11) Mean, SD and n provided by author.

Figure 3.5. Meta-analysis of effect of interventions on DBP

**3.3.3.3 Publication bias**

SBP. The *p* value for Eggers test (Egger, Smith, Schneider, & Minder, 1997) was 0.02 which suggests that significant publication bias is likely (Sedgwick, 2013). The funnel plot can be seen in Figure 3.6

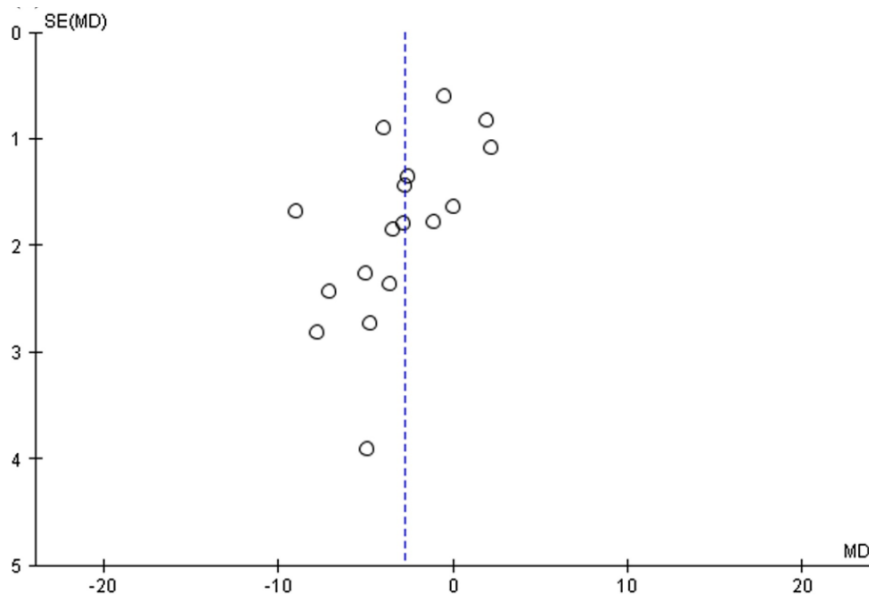


Figure 3.6. Funnel plot for SBP

DBP. The  $p$  value for Eggers test (Egger et al., 1997) was 0.27 so it was concluded that symmetry exists in the funnel plot. Therefore it is concluded that bias does not exist in the studies included in the meta-analysis (Sedgwick, 2013). The funnel plot can be seen in Figure 3.7.

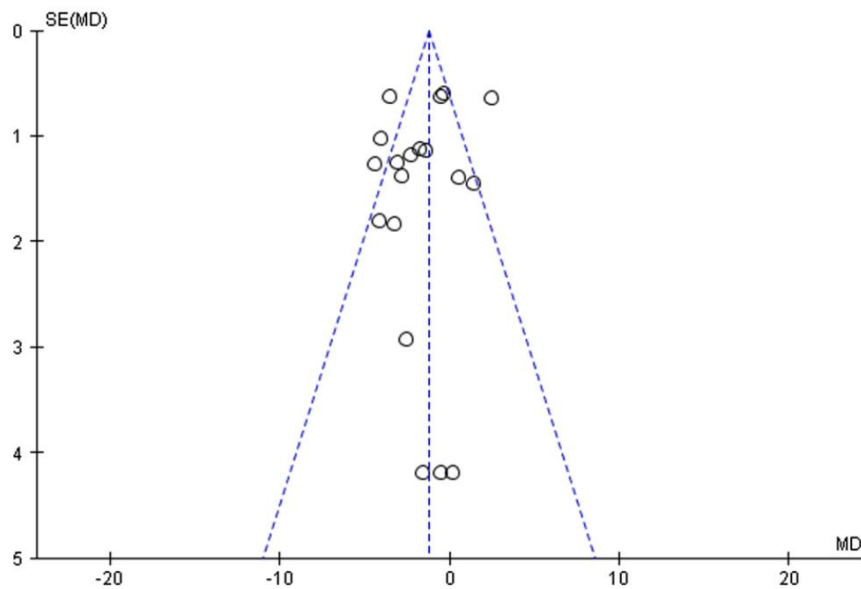


Figure 3.7. Funnel plot for DBP

#### 3.3.3.4 Subgroup Analysis

According to our protocol, five subgroup analyses were undertaken. As 10 of the included 26 studies involved home BP monitoring we also included a posthoc subgroup analysis on this.

Technological interventions. The most common technological component seen was telephone calls. Involvement of technology was not significantly associated with effect on SBP ( $\chi^2 = 1.10$ ,  $df = 1$ ,  $p = 0.29$ ,  $I^2 = 9.0\%$ ) but was significantly associated with effect on DBP ( $\chi^2 = 10.12$ ,  $df = 1$ ,  $p = 0.001$ ,  $I^2 = 90.1\%$ ). However heterogeneity is extremely high for the DBP outcome.

Combination pill interventions. Three studies used combination pills but data could not be extracted for any of these. As a result they are not present in the meta-analyses.

Service provision interventions. Nine studies had interventions that involved service providers – 2 included physicians, 3 included nurses and 4 included pharmacists. These interventions involved a service provider being trained in a particular intervention technique (e.g. motivation interviewing). The service providers then delivered the intervention to the patient. Involvement of service providers was not significantly associated with effect on SBP ( $\chi^2 = 0.12$ ,  $df = 1$ ,  $p = 0.73$ ,  $I^2 = 0\%$ ) or DBP ( $\chi^2 = 0.15$ ,  $df = 1$ ,  $p = 0.70$ ,  $I^2 = 0\%$ ).

Low adherers. Two studies targeted non-adherers and DBP was the only common outcome. Targeting low adherence was not significantly associated with effect ( $\chi^2 = 0.04$ ,  $df = 1$ ,  $p = 0.84$ ,  $I^2 = 0\%$ ).

Patient subgroup analysis. A subgroup analysis on age is not warranted as age criteria is homogenous across studies. Similarly, only one study targeted gender so subgroup analysis is not warranted.

Home BP monitoring. The use of home BP monitoring was not significantly associated with effect on SBP ( $\chi^2 = 0.00$ ,  $df = 1$ ,  $p = 0.99$ ,  $I^2 = 0\%$ ) but was significantly associated with

effect on DBP ( $\chi^2 = 5.21$ ,  $df = 1$ ,  $p = 0.02$ ,  $I^2 = 80.8\%$ ). However as in the case of technological interventions, heterogeneity is extremely high for the DBP outcome.

### **3.3.3.5 Sensitivity Analysis**

All studies showed a relatively high risk of bias in some domains, so we conducted a sensitivity analysis of the 8 studies where the sequence generation and allocation concealment scored as low risk of bias versus unclear or with a high risk of bias. These aspects of bias apply to the trial as a whole rather than being inherently specific to different outcomes within the trial (Higgins et al., 2011). We found that the effect of adherence interventions on both SBP (MD = -4.04 mmHg; 95% CI [-5.89 to -2.19];  $I^2 = 54\%$ ) and DBP (MD = -2.73 mmHg; 95% CI [-3.65 to -1.81];  $I^2 = 39\%$ ) remained significant ( $p < 0.001$ ).

### **3.3.3.6 Trials for which we could not extract data**

Among trials for which we could not extract data on SBP or DBP outcomes, Baird et al. (1984), Becker et al. (1986), Matsumura et al. (2012), Girvin, McDermott, and Johnston (1999), G. Ogedegbe et al. (2014) and Sackett et al. (1975) did not find statistically significant effects on BP outcomes. Friedman et al. (1996) reported a statistically significant effect on both SBP and DBP.

### **3.3.3.7 Secondary outcomes**

The secondary outcome of adherence was specified *a priori* in the study protocol. Due to the heterogeneity of adherence measures it was not feasible to pool effects. The 2014 review by Nieuwlaat et al. (2014) cited the meta-analysis reported by the Ascertain Barriers for Compliance (ABC) project team, which exclusively focused on RCTs that measured adherence by means of MEMS and still found a very high heterogeneity of effects ( $I^2 = 98.88\%$ ) (Demonceau et al., 2013) to come to the same conclusion. Instead we conducted a narrative review of adherence outcomes.

Self report. Self-report was the most common adherence measure. This usually took the form of an adherence scale. Adherence scales are simple and easy to use and can effectively measure adherence (Haynes et al., 1980; Walsh, Mandalia, & Gazzard, 2002) but their subjective nature means that they can potentially be problematic. In particular reporting biases such as ‘recall and social desirability biases’ may influence measurement in some contexts

Morisky Medication Adherence Scale. The Morisky Medication Adherence Scale is one of the most frequently used scales to measure adherence. It was first developed by Morisky, Green, and Levine (1986) as a four item measure – the MMAS-4. It has been validated in patients with low literacy and across a wide range of diseases and so is one of the most widely used scales for research (Culig & Leppée, 2014). Based on the MMAS-4, Morisky, Ang, Krousel-Wood, and Ward (2008) developed the 8-item MMAS (MMAS-8). The additional items focus on medication-taking behaviours, especially related to underuse, such as forgetfulness, for clearer identification of barriers to adherence (Tan, Patel, & Chang, 2014). Six of the 26 included studies used either the MMAS-4 or the MMAS-8 (Amado Guirado et al., 2011; Friedberg et al., 2015; Morgado, Rolo, & Castelo-Branco, 2011; Ogedegbe et al., 2014; Stewart et al., 2014; Wong et al., 2013). Of these, only Morgado et al. (2011) reported a significant difference between groups at follow-up. While Stewart et al. (2014) did not find a main effect on the MMAS outcome, a subgroup analysis found that there was a significant difference between those who were non adherent at baseline.

Other adherence scales. While the MMAS is commonly used, it is just one of many of adherence scales. Nguyen, Caze, and Cottrell (2014) have identified 43 validated self-report adherence scales, excluding those that were not in English. Four of the studies in this review use various other adherence scales. Greer and Ostwald (2015) measured adherence using the Hill-Bone Compliance to High Blood Pressure Therapy (HBCHBPT) scale (Kim, Hill, Bone,

& Levine, 2000). This scale ranges from 14 (perfect adherence) to 56 (non adherent). There was no difference between the intervention and control groups on the HBCHBPT at six month follow-up. Ma, Zhou, Zhou, and Huang (2014) measured adherence using the Treatment Adherence Questionnaire of Patient with Hypertension (TAQPH) (Ma, Chen, You, Luo, & Xing, 2012). This test contains 28 items grouped into six factors: medication, diet, exercise, weight control, stimulation and relieving stress. There was a significant difference between the intervention and control group scores on the medication subscale of the TAQPH at six month follow up. Tinsel et al. (2013) used the Medication Adherence Rating Scale (MARS-D). The MARS-D contains 10 items to evaluate the patients adherence behaviour, attitude towards medication and general disease control (Thompson, Kulkarni, & Sergejew, 2000). There was no difference between the intervention and control group scores on the MARS-D at six month follow up. However the authors note that the mean MARS-D score at baseline was quite high – leaving little potential for improvement.

Other self-report measures. Two studies did not use a validated adherence scale to measure adherence but rather used patient interviews. This can be a low cost and simple to use subjective method to assess adherence (Farmer, 1999). However, as with adherence scales, their subjective nature, along with possible social pressures means they can be problematic.

Becker et al. (1986) randomised 171 patients to a special packaging intervention or a usual care control group. Adherence was measured by asking patients a nonthreatening, non-judgmental question about their compliance behaviour. Those who admitted less than perfect compliance were considered noncompliant. There was no difference between the intervention and control groups in compliance answers at six month follow up. In the study by Margolius et al. (2012) adherence was measured by health coaches during the weekly phonecalls. They asked patients to report the number of days in the past week that they missed taking a blood

pressure medication. There was no difference in the amount of missing pills reported between the intervention and control groups at six month follow-up.

MEMS™. Medication event monitoring systems (MEMS™) are medication bottle caps with a microprocessor that records the occurrence and time of each bottle opening. It generates more data than self-report measures as it can identify whether non-adherence is consistent or sporadic and can also detail the number of daily doses on any partial adherence situation (Farmer, 1999). This, along with its objective nature means that MEMS are frequently used as a reference standard for validating other adherence measures (Lam & Fresco, 2015), although a pill bottle opening does not necessarily mean that the patient took the prescribed dose.

Six of the included studies used MEMS (Dusing et al., 2009; Girvin et al., 1999; Marquez-Contreras, Martell-Claros, Gil-Guillen, de la Figuera-Von Wichmann, Casado-Martinez, Martin-de Pablos, Figueras, Galera, & Serra, 2006; Ogedegbe et al., 2012; Rudd et al., 2004; Schroeder, Fahey, Hollinghurst, & Peters, 2005). Of these, three (Girvin et al., 1999; Marquez-Contreras, Martell-Claros, Gil-Guillen, de la Figuera-Von Wichmann, Casado-Martinez, Martin-de Pablos, Figueras, Galera, & Serra, 2006; Ogedegbe et al., 2012) found that the intervention significantly improved adherence rates as measured by MEMS.

Pill count. Pill counts are an objective and indirect measure which count the number of pills that have been consumed between two appointments. This number is then compared to the total number of pills that the patient received to calculate an adherence ratio (Farmer, 1999). Although this method is based on a similar premise to MEMS (removal of a pill is equivalent to its consumption), pill counts do not generate a medication taking pattern as MEMS does.

Of the included studies, 11 used a pill count as measure of adherence (Amado Guirado et al., 2011; Baird et al., 1984; Becker et al., 1986; Friedman et al., 1996; Girvin et al., 1999;

Haynes et al., 1976; Hosseininasab et al., 2014; Johnson, Taylor, Sackett, Dunnett, & Shimizu, 1978; Marquez Contreras et al., 2005; Matsumura et al., 2012; Sackett et al., 1975). Of these, five found a significant difference between the groups at follow up in adherence ratio as calculated by pill count ((Baird et al., 1984; Friedberg et al., 2015; Haynes et al., 1976; Hosseininasab et al., 2014; Marquez Contreras et al., 2005) However in the case of Hosseininasab et al. (2014) the authors note that although the difference was statistically significant they prefer not to interpret it as a clinically relevant results as adherence rates were >95% in both groups at follow up, and the difference between the groups was quite small at 2%.

Pharmacy refill records. Using pharmacy refill records as a measure of adherence assumes that the patients prescription-refilling patterns correspond the patients medication taking behaviour (Lam & Fresco, 2015). It also assumes that the medication has been taken as prescribed and thus partial adherence cannot be observed (Steiner & Prochazka, 1997). As a result, refill records are not seen as robust a measure as MEMS.

Only one study of the 26 used pharmacy refill records. Svarstad et al. (2013) investigated an augmented pharmacy service intervention and found it to have an effect on refill adherence at follow up.

More than one measure. Three studies included more than one measure. Amado Guirado et al. (2011) and Becker et al. (1986) used self-report and pill count. Both measures found the same result in both studies. Girvin et al. (1999) used pill count and MEMS. There was a significant difference in medication adherence between the groups at follow up according to the MEMS data, but no difference in the adherence ratio as measured by pill count.

A summary of findings for all adherence outcomes can be seen in Table 3.1.

### **3.3.3.8 Theoretical domains framework**

The coding for the domains targeted in the intervention and control groups for each of the studies is shown in Appendix IV.

Table 3.2 presents the number of times each of the domains was coded in the intervention group of each of the studies.

Table 3.2.

Number of times each of the domains was coded in the *intervention* group of each of the studies.

	Amado 2011	Baird 1984	Becker 1986	Dusing 2009	Friedberg 2014 Int 1	Friedberg 2014 Int 2	Friedman 1996	Girvin 1999	Greer 2014	Haynes 1976	Hosseininasab 2014	Johnson 1978 Int 1	Johnson 1978 Int 2
Domain													
1. Knowledge	1			1	1	2	1		1		1		
2. Skills													
3. Social /professional role and identity													
4. Beliefs about capabilities					1								
5. Optimism													
6. Belief about consequences	1			1	2	1	1						
7. Reinforcement										1			
8. Intentions					1								
9. Goals													
10. Memory, attention and decision processes	2	2	2	2	2	1	2	2	1	1	1	2	1
11. Environmental context and resources	1	1	1	1		1	1	1	2	1	1	1	1
12. Social influences	1			2	1	1	1		1	1	1	2	
13. Emotion													
14. Behavioural regulation	1			1	1		1			1	1	1	1
<b>Total no of domains targeted</b>	<b>7</b>	<b>3</b>	<b>3</b>	<b>8</b>	<b>9</b>	<b>6</b>	<b>7</b>	<b>3</b>	<b>5</b>	<b>5</b>	<b>5</b>	<b>6</b>	<b>3</b>

	Johnson 1978 Int 3	Ma 2013	Margolius 2012	Marquez Contreras 2005 Int 1	Marquez Contreras 2005 Int 2	Marquez Contreras 2006	Matsumura 2012	Morgado 2011	Ogedegbe 2012	Ogedegbe 2014	Rudd 2004	Sackett 1975 Int 1	Sackett 1975 Int 2	Schroeder 2005	Stewart 2015	Svarstad 2013	Tinsel 2014	Wong 2013	
Domain																			
1. Knowledge		1			1			1	1	1	1		1		1	2	1	1	
2. Skills		2															1		
3. Social /professional role and identity																	1		
4. Beliefs about capabilities		1																	
5. Optimism																			
6. Belief about consequences		1		1	1			1		1			1	1	1	1	1	1	
7. Reinforcement				1												1			
8. Intentions																			
9. Goals		1						1	1						1	1		1	
10. Memory, attention and decision processes	1	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	2	1	1
11. Environmental context and resources		2	1		1	1	1	1	1	1	1	1	1		2	5	1	2	
12. Social influences	2	2	1	1				1	1	1	1			1	1	1	1	2	
13. Emotion		1							1										
14. Behavioural regulation		2	1	1		1		1	1	1	1				1	1			
<b>Total no of domains targeted</b>	<b>2</b>	<b>15</b>	<b>5</b>	<b>6</b>	<b>5</b>	<b>4</b>	<b>3</b>	<b>8</b>	<b>8</b>	<b>6</b>	<b>6</b>	<b>2</b>	<b>5</b>	<b>4</b>	<b>8</b>	<b>14</b>	<b>7</b>	<b>8</b>	

The domain coded most frequently was ‘memory, attention and decision processes’ (31 out of 31 interventions, coded 51 times). The second most frequently coded domain was ‘environmental context and resources’ (27 out of 31 interventions; coded 34 times), followed by ‘social influences’ (22 of 31 interventions; coded 24 times), ‘knowledge’ (20 out of 31 interventions, coded 18 times), ‘behavioural regulation’ (18 of 31 interventions; coded 19 times) and then ‘beliefs about consequences’ (17 of 31 interventions; coded 17 times). There was only one domain that was never coded: ‘optimism’. The remaining seven domains (‘skills’; ‘beliefs about capabilities’ ‘social and professional role/identity’; ‘reinforcement’; ‘intentions’ ‘goals’; and ‘emotion’) were coded six or less times.

Table 3.3 presents the number of times each of the domains was coded in the control groups of each of the studies.

Table 3.3.

*Number of times each of the domains was coded in the **control** group of each of the studies.*

	Amado 2011	Baird 1984	Becker 1986	Dusing 2009	Friedberg 2014	Friedman 1996	Girvin 1999	Greer 2014	Haynes 1976	Hosseininasab 2014	Johnson 1978
Domain											
1. Knowledge					1						
2. Skills											
3. Social /professional role and identity											
4. Beliefs about capabilities											
5. Optimism											
6. Belief about consequences					1						
7. Reinforcement											
8. Intentions											
9. Goals											
10. Memory, attention and decision processes			1		1						
11. Environmental context and resources			1								
12. Social influences											
13. Emotion											
14. Behavioural regulation											
Total no of domains targeted	0	0	2	0	3	0	0	0	0	0	0

	Ma 2013	Margolius 2012	Marquez Contreras 2005	Marquez Contreras 2006	Matsumura 2012	Morgado 2011	Ogedegbe 2012	Ogedegbe 2014	Rudd 2004	Sackett 1975	Schroeder 2005	Stewart 2015	Svarstad 2013	Tinsel 2014	Wong 2013
Domain															
1. Knowledge	1						1	1					1		1
2. Skills															
3. Social /professional role and identity															
4. Beliefs about capabilities															
5. Optimism															
6. Belief about consequences													1		1
7. Reinforcement															
8. Intentions															
9. Goals							1								
10. Memory, attention and decision processes	1	2					2	1					1		
11. Environmental context and resources	1	1					1	1					1		
12. Social influences		1					1								
13. Emotion															
14. Behavioural regulation		1					1								
Total no of domains targeted	3	5	0	0	0	0	7	3	0	0	0	0	4	0	2

We identified and coded domains for only ten of the control conditions. This was due to most of the control conditions simply being described as ‘usual care’. Fewer domains and fewer elements within these were coded. The domains most frequently identified in the description of the control group were ‘memory, attention and decision processes’ (9 of 26 control groups; coded 11 times), ‘knowledge’ (6 of 26 control groups; coded 6 times) ‘environmental context and resources’ (6 of 26 control groups; coded 6 times). ‘Beliefs about consequences’, ‘social influences’ and ‘behavioural regulation’ were coded three or less times.

Relationship between total number of times the domains are coded within an intervention and effect size. Table 3.4 summarises the total number of times the domains were coded, for each study intervention and control group.

Table 3.4

*Total number of times domains coded within intervention and control groups*

Studies	Total no of times any domain coded - Intervention	Total no of times any domain coded - Control	Intervention minus control
Amado 2011	7	0	7
Baird 1984	3	0	3
Becker 1986	3	2	1
Dusing 2009	8	0	8
Friedberg 2014 Intervention 1	9	3	6
Friedberg 2014 Intervention 2	6	3	3
Friedman 1996	7	0	7
Girvin 1999	3	0	3
Greer 2014	5	0	5
Haynes 1976	5	0	5
Hosseininiasab 2014	5	0	5
Johnson 1978 Intervention 1	6	0	5
Johnson 1978 Intervention 2	3	0	3
Johnson 1978 Intervention 3	3	0	3
Ma 2013	15	3	12
Margolius 2012	5	5	0

Marquez Contreras 2005 Intervention 1	6	0	6
Marquez Contreras 2005 Intervention 2	5	0	5
Marquez Contreras 2006	4	0	4
Matsumura 2012	3	0	3
Morgado 2011	8	0	8
Ogedegbe 2012	8	7	1
Ogedegbe 2014	6	3	3
Rudd 2004	6	0	6
Sackett 1975 Intervention 1	2	0	2
Sackett 1975 Intervention 2	5	0	5
Schroeder 2005	4	0	4
Stewart 2015	9	0	8
Svarstad 2013	14	4	10
Tinsel 2014	7	0	7
Wong 2013	8	2	6

The relationship between the total number of times the domains were coded within an intervention and change of SBP ( $r = -0.234, p = .335$ ) and DBP was not significant ( $r = -0.080, p = .732$ ). The sensitivity analysis (not subtracting the number of control group domains) showed similar results (SBP:  $r = -.445, p = 0.056$ ; treatment:  $r = -.204, p = 0.376$ ).

Relationship between the number of different domains coded within an intervention and the effect size. Table 3.5 summarises the total number of times different domains were coded, for each study intervention and control group.

Table 3.5.

*Total number of times **different** domains were coded in intervention and control groups*

Studies	Total no of times any domain coded - Intervention	Total no of times any domain coded - Control	Intervention minus control
Amado 2011	6	0	6
Baird 1984	2	0	2

Becker 1986	2	2	0
Dusing 2009	6	0	6
Friedberg 2014 Intervention 1	7	3	4
Friedberg 2014 Intervention 2	6	3	3
Friedman 1996	6	0	6
Girvin 1999	2	0	2
Greer 2014	5	0	5
Haynes 1976	5	0	5
Hosseinasab 2014	5	0	5
Johnson 1978 Intervention 1	4	0	4
Johnson 1978 Intervention 2	3	0	3
Johnson 1978 Intervention 3	2	0	2
Ma 2013	10	3	7
Margolius 2012	4	4	0
Marquez Contreras 2005 Intervention 1	5	0	5
Marquez Contreras 2005 Intervention 2	4	0	4
Marquez Contreras 2006	3	0	3
Matsumura 2012	2	0	2
Morgado 2011	7	0	7
Ogedegbe 2012	7	6	1
Ogedegbe 2014	6	3	3
Rudd 2004	5	0	5
Sackett 1975 Intervention 1	2	0	2
Sackett 1975 Intervention 2	4	0	4
Schroeder 2005	3	0	3
Stewart 2015	7	0	7
Svarstad 2013	8	4	4
Tinsel 2014	7	0	7
Wong 2013	6	2	4

The relationship between the total number of times different domains were coded within an intervention and change of SBP ( $r = 0.080, p = .746$ ) and DBP was not significant ( $r = -0.188, p = .415$ ). The sensitivity analysis (not subtracting the number of control group domains) showed similar results (SBP:  $r = -.267, p = 0.268$ ; DBP:  $r = -.050, p = 0.828$ ).

Subgroup analysis. In addition to the analysis set out in the protocol, we conducted a further subgroup analysis on the effect of presence or absence of individual domains (Tables 3.6 and 3.7).

Table 3.6.

*Subgroup analysis of TDF*

*SBP*

TDF Domain	N	MD	95% CI	<i>p</i>	I <sup>2</sup>
<b>Knowledge</b>					
Applied	8	-2.02	-4.15, 0.10	0.06	85%
Not Applied	9	-3.60	-5.53, -1.67	<0.001	80%
Test for subgroup differences				0.28	
<b>Beliefs about capabilities</b>					
Applied	2	-3.76	-7.03, -0.49	0.02	0%
Not Applied	14	-2.72	-4.36, -1.07	<0.001	82%
Test for subgroup differences				0.58	
<b>Beliefs about consequences</b>					
Applied	8	-2.38	-4.98, 0.22	<0.001	84%
Not Applied	9	-3.27	-5.30, -1.24	0.002	75%
Test for subgroup differences				0.60	
<b>Reinforcement</b>					
Applied	2	-5.84	-11.90, 0.23	0.005	87%
Not Applied	15	-2.28	-3.78, -0.78	0.003	75%
Test for subgroup differences				0.27	
<b>Goals</b>					

Applied	3	-4.34	-9.08, 0.41	0.07	80%
Not Applied	13	-2.36	-3.95, -0.78	0.004	78%
Test for subgroup differences				0.44	
<b>Memory, attentions and decision processes</b>					
Applied	12	-1.93	-3.55, -0.31	<0.001	78%
Not Applied	5	-5.15	-7.69, -2.60	0.11	47%
Test for subgroup differences				0.04	
<b>Environmental context</b>					
Applied	12	-2.04	-3.60, -0.47	<0.001	77%
Not Applied	5	-5.47	-8.77, -2.16	0.001	62%
Test for subgroup differences				0.07	
<b>Social influences</b>					
Applied	12	-2.06	-3.63, -0.48	<0.001	77%
Not Applied	5	-5.38	-8.82, -1.94	0.03	66%
Test for subgroup differences				0.08	
<b>Behavioural regulation</b>					
Applied	10	-3.34	-5.44, -1.25	<0.001	83%
Not Applied	7	-2.00	-4.38, -1.27	0.003	70%
Test for subgroup differences				0.41	

Table 3.7.

*Subgroup analysis of TDF**DBP*

TDF Domain	N	MD	95% CI	<i>p</i>	I <sup>2</sup>
<b>Knowledge</b>					
Applied	8	-0.75	-1.30, 0.81	0.008	87%
Not Applied	11	-2.46	-3.36, -0.19	<0.001	12%
Test for subgroup differences				0.001	
<b>Beliefs about consequences</b>					
Applied	8	-0.78	-1.39, -0.17	0.01	88%
Not Applied	11	-1.85	-2.59, -1.11	<0.001	21%
Test for subgroup differences				0.03	
<b>Reinforcement</b>					
Applied	3	-4.04	-5.48, -2.61	<0.001	0%
Not Applied	16	-0.87	-1.38, -0.37	0.0006	75%
Test for subgroup differences				<0.001	
<b>Goals</b>					
Applied	3	-1.98	-3.27, -0.69	0.003	69%
Not Applied	16	-1.10	-1.61, -0.59	<0.001	79%
Test for subgroup differences				0.22	
<b>Memory, attentions and decision processes</b>					
Applied	16	-1.17	-1.65, -0.69	<0.001	78%
Not Applied	3	-3.53	-5.08, -1.98	<0.001	0%
Test for subgroup differences				0.004	
<b>Environmental context</b>					
Applied	14	-0.84	-1.35, -0.34	0.001	78%
Not Applied	5	-3.69	-4.99, -2.39	<0.001	0%
Test for subgroup differences				<0.001	
<b>Social influences</b>					

Applied	14	-0.92	-1.43, -0.41	0.0004	80%
Not Applied	5	-3.11	-4.39, -1.84	<0.001	0%
Test for subgroup differences				0.002	
<b>Behavioural regulation</b>					
Applied	12	-1.88	-2.45, -1.32	<0.001	68%
Not Applied	7	0.34	-0.52, 1.21	0.44	76%
Test for subgroup differences				<0.001	

A domain was considered present if it was coded in the intervention group only. The only domain to influence effect on both SBP ( $\chi^2 = 4.37$ ,  $df = 1$ ,  $p = 0.04$ ,  $I^2 = 77.1\%$ ) and DBP ( $\chi^2 = 8.11$ ,  $df = 1$ ,  $p = 0.004$ ,  $I^2 = 87.7\%$ ) was ‘memory, attention and decision processes’. However, ‘beliefs about consequences’ ( $\chi^2 = 4.79$ ,  $df = 1$ ,  $p = 0.03$ ,  $I^2 = 79.1\%$ ), ‘reinforcement’ ( $\chi^2 = 16.77$ ,  $df = 1$ ,  $p < 0.001$ ,  $I^2 = 94\%$ ), ‘environmental context and resources’ ( $\chi^2 = 16.05$ ,  $df = 1$ ,  $p < 0.001$ ,  $I^2 = 93.8\%$ ), ‘social influences’ ( $\chi^2 = 9.82$ ,  $df = 1$ ,  $p = 0.002$ ,  $I^2 = 89.8\%$ ) and ‘behavioural regulation’ ( $\chi^2 = 17.91$ ,  $df = 1$ ,  $p < 0.001$ ,  $I^2 = 94.9\%$ ) all influenced effect on DBP only. Heterogeneity is extremely high across all of these subgroups.

### 3.4 Discussion

#### 3.4.1 Summary of Main Results

Overall the meta-analysis found a modest main effect on SBP (MD -2.71mmHg, 95% CI -4.17 to -1.26,  $I^2=77\%$ ) and DBP (MD -1.25 mmHg, 95% CI -1.72 to -0.79,  $I^2= 74\%$ ). The sensitivity analysis with the 8 studies that had a low risk of bias for randomisation and allocation sequence revealed that the reduction in BP was larger (SBP; MD = -4.04 mmHg; 95% CI 5.89 TO -2.19,  $I^2=54\%$ ; DBP; MD = -2.73 mmHg; 95% CI -3.65 to -1.81,  $I^2=39\%$ ). Although heterogeneity remained significant there was a substantial reduction. These findings suggest that behavioural interventions that attempt to improve adherence to anti-

hypertensive medication have the potential to significantly lower blood pressure by a magnitude that is likely to be clinically significant in terms of cardiovascular risk reduction. There are, however, a number of important limitations to what the analyses of these studies can tell us which will be discussed in the following sections.

#### **3.4.1.1 Adherence**

Due to the heterogeneity of adherence measures it was not feasible to pool effect sizes for the measures of behaviour. We conducted a narrative review by outcome measure. Twelve of the included studies reported a statistically significant effect of the interventions on adherence. This is a similar success rate to that found in the 2014 review by Nieuwlaat et al. (2014). However as discussed by Nieuwlaat et al. (2014), this method of ‘vote counting’ means we cannot assume that these numbers reflect the actual proportion of studies that had an important effect using the TDF.

#### **3.4.1.2 Theoretical Domains Framework**

We conducted a theory based analysis of the interventions from the 26 included studies. As has been frequently observed in the behaviour change literature (e.g. (Michie, Fixsen, Grimshaw, & Eccles, 2009; Riley et al., 2008), many studies did not report the content of the interventions and in particular, the control groups, in sufficient detail (de Bruin, Viechtbauer, Hospers, Schaalma, & Kok, 2009). This resulted in some coding difficulties and it is possible that, in some cases, the content of studies may not have been accurately captured using the TDF.

The six key domains that appeared to be targeted most frequently by interventions were: ‘Memory, attention and decision processes’, ‘environmental context and resources’, social influences’, ‘knowledge’, ‘behavioural regulation’ and ‘beliefs about consequences’. The quantitative analysis suggested that there was no relationship between both the number of times the domains were coded and the number of different domains coded and the effect size

of the intervention on both SBP and DBP. This suggests that the complexity of interventions as measured by the range of domains targeted is not clearly associated with greater effectiveness in terms of reductions in blood pressure.

We conducted a further exploratory subgroup analysis on each of the domains. The only domain associated with a larger effect on both SBP and DBP was ‘memory, attention and decision processes’. However, this domain was present in most studies and the absence of some targeting of this domain might reflect minimal intensity interventions that are likely to have little impact on adherence and blood pressure outcomes. ‘Beliefs about consequences’ ‘reinforcement’ ‘environmental context and resources’ ‘social influences’ and ‘behavioural regulation’ were all associated with larger effect on DBP only. These domains may therefore represent important targets for intervention development.

### **3.4.2 Overall completeness and applicability of the evidence**

We were unable to include data from 9 of the included studies in the meta-analysis due to limitations in the data available. This is a limitation of the data that may introduce bias in the present analysis, however, the meta-analysis on SBP included 19 interventions and the meta-analysis on DBP contained 21. All trials included patients with a confirmed diagnosis of hypertension. Therefore it would seem that the findings are largely applicable to hypertensive patients and the quantity of studies used compares favourably with recent similar reviews of adherence interventions in chronic conditions such as Type 2 diabetes where there is a similar continuous objective clinical outcome (K = 10 in Zomahoun et al., 2015).

However, 25 of the 26 included studies were conducted in a high income country. The prevalence of hypertension is significantly higher in low and middle income countries. In 2010, 28.5% of adults had hypertension in high income countries, compared to 31.5% in low and middle income countries and between 2000 and 2010 the prevalence of hypertension

decreased by 2.6% in high-income countries but increased by 7.7% in low- and middle-income countries (Mills et al., 2016). As a result, the included studies cannot be seen as globally representative. Also, in their systematic analysis of population based studies on hypertension, Mills et al. (2016) argue that there has been a substantial increase in hypertension awareness, treatment and control in high income countries, which has not been seen in middle and lower income countries. This highlights a need for high quality interventions on adherence (and other aspects of hypertension) at an international level, that can be tailored to different settings.

### **3.4.3 Quality of the evidence**

As we aimed to include only the highest quality RCTs, inclusion in this review required meeting stringent inclusion criteria, including at least 80% follow up at six months. A sufficient number of trials (SBP: n = 19, DBP: n = 21) and a large sample size (SBP: n = 5643, DBP: n = 5301) were available to generate meaningful meta-analyses and allowed several subgroup analyses.

However, the quality of the studies varied, and only 8 of the 26 studies were deemed to have a low risk of bias for randomisation and allocation sequence generation. This may not be an exact reflection of the study quality though as many papers did not provide sufficient detail for the risk of bias to be accurately determined. This is reflected in the ‘moderate’ and ‘fair’ levels of agreement reached when determining risk of bias. As a consequence, it is possible that some of the RCTs had a lower risk of bias than we had determined and should have been included in the sensitivity analysis. Similar difficulties emerged when coding interventions with the TDF. Our coding had to be based on inference from the text, as very few studies reported the explicit use of theory. As mentioned previously, many studies did not report the intervention and control group content in detail. For example, Stewart et al. (2014) and Tinsel

et al. (2013) both mention motivational interviewing as part of their interventions, but do not provide information on its exact components. Most studies reported the control condition to be simply ‘usual care’. de Bruin et al. (2009) developed a tool to assess standard care quality in adherence interventions and found that it varied considerably between reviewed studies and was significantly related to clinically relevant variations in treatment success rates. Accordingly, de Bruin et al. (2016) argue that that when presenting information on what interventions and intervention components work, it is crucial to take variability in the comparison groups into account. As the included studies in our review span over 40 years and several different countries, there is no doubt that there is variability in the ‘usual care’ control conditions, due to the changing patterns of routine clinical management of hypertension over this time.

Another challenge that arose when coding with the TDF was the relationship between domains. Not all constructs fall into distinct domains, for example, ‘action planning’ is a construct in both ‘goals’ and ‘behavioural regulation’. This problem has been identified by Little et al. (2015) when trying to clarify the boundaries between some domains when using the TDF as a coding framework. Therefore while the TDF is a useful tool for examining the content of interventions the discriminant validity of some of the domains may need refinement.

There was substantial heterogeneity in the main effect findings which could reflect heterogeneity in either the methods used in the trials, the interventions themselves or the patient populations. The possible modifying effects of different intervention types were evaluated by subgroup analysis. All except home BP monitoring and technological interventions were not associated with effect sizes and heterogeneity remained extremely high in both significant subgroup analyses. It therefore seems unlikely that the intervention type alone explains the observed heterogeneity.

### **3.4.5 Potential biases in the review process**

We conducted the review to Cochrane standard. Two authors screened papers, extracted data, assessed risk of bias and coded interventions with the TDF. A third author adjudicated across all work. The literature search was comprehensive and included several databases, trial registries and reference lists of included trials. As with Nieuwlaat et al. (2014) we chose our eligibility criteria to summarise the current best evidence of unconfounded RCTs, with at least 80% follow up in all treatment groups, assessing the effect on both clinical and adherence outcomes. It is possible that the results may have been different if a larger loss to follow up was allowed.

Publication bias was evident in the studies that reported a SBP outcome. This implies that the estimate of effect may not be accurate and if unpublished studies were to be included. The modest reduction in SBP may diminish or not be seen at all in an unbiased set of studies (Hopewell, Loudon, Clarke, Oxman, & Dickersin, 2009).

### **3.4.6 Agreements or disagreements with other studies or reviews**

Nieuwlaat et al. (2014) concluded that interventions to enhance medication adherence across all conditions were 'complex and not very effective'. This update, specific to adherence in the content of hypertension medication and inclusive of a meta-analysis on the clinical outcome of BP, potentially lends quantitative support to this conclusion. The effect on SBP and DBP, although statistically significant, appear quite modest in terms of clinical significance and had substantial heterogeneity and less than half the included studies reported a significant effect on adherence outcomes. Network meta-analysis using the current data and meta-analysis of other efficacious hypertension interventions e.g. exercise, diet etc. may help to establish the comparative effectiveness of adherence support interventions in the absence of head-to-head trials with other approaches to lower blood pressure. These kinds of studies are becoming

increasingly important in healthcare decision making particularly in terms of evaluating the likely return of behavioural versus biomedical intervention (Naci & Ioannidis, 2013). It is important to acknowledge that some of the adherence interventions in studies included in this review may have been multi-factorial and may have explicitly or implicitly tried to influence other behaviours that are known to reduce blood pressure, therefore it is challenging to disentangle the unique effects of medication adherence interventions.

Conn et al. (2015) conducted a similar review and meta-analysis on interventions to enhance adherence in hypertension, but focused on the adherence rather than the clinical outcomes. As a result, they were able to include 101 studies in the review and found a significant effect (mean standardised effect size of 0.3) on adherence outcomes. Although it is difficult to compare across a heterogeneous range of measurement approaches, higher adherence is associated with higher odd of BP control (Ho, Bryson, & Rumsfeld, 2009) and so the modest effect size on adherence outcomes found by Conn et al. (2015) seems to be in line with the modest effect size on BP outcomes found in this review.

Khatib et al. (2014) examined patient and healthcare provider barriers to hypertension awareness, treatment and follow-up in both quantitative and qualitative studies using the TDF. In the qualitative studies, healthcare providers most commonly reported barriers to do with lack of resources and time. Patients reported barriers related to distance and transportation to health care centres. According to our theoretical analysis of the included studies, these availability barriers were not frequently targeted in interventions. In contrast, quantitative studies focused on barriers to do with knowledge and professional identity among providers, and barriers related to beliefs about treatment consequences and side effects of medications with patients. Once again, constructs around professional identity were not frequently seen in the included studies. However, beliefs about treatment consequences tended to be a common component of the included adherence interventions.

### **3.4.7 Implications for practise**

At the outset of this review, we aimed to identify whether the targeting of particular theoretical domains is associated with greater effect sizes in adherence interventions in hypertension, leading to suggestions for practise. However, a paucity of intervention detail meant that this analysis was limited. The only domain that emerged as being associated with effect on both SBP and DBP was ‘memory, attention and decision processes’ and this was coded in every intervention – as taking part in an adherence intervention focuses the patients’ behaviour. Therefore, there does not appear to be any particular domain that is associated with more effective adherence interventions; however there are limitations to the conclusions regarding intervention approaches that we can draw from this analysis due to the limited specification of interventions that we have already discussed.

### **3.4.8 Implications for research**

Of the 26 included studies, only 6 used MEMs – the ‘gold standard’ of adherence outcomes (Lam & Fresco, 2015). Future research needs to move towards consistently using objective adherence outcomes to reduce the threat of measurement biases. One of the greatest challenges of this review was assessing risk of bias, extracting sufficient data to calculate effect size and coding interventions with the amount of information provided in papers. Several reviews in the adherence literature (Conn et al., 2015; Gwadry-Sridhar et al., 2013; Nieuwlaat et al., 2014) have identified this in the past and it is imperative that future research comprehensively reports methodology.

The absence of clear theory from behavioural sciences in the development of these adherence interventions is also a fundamental problem that prevents progress in this area of research. Using theory can help refine intervention design and promote more accurate description and analysis of intervention effects. This will facilitate the identification of effective intervention

components. This will ultimately allow researchers to provide clearer syntheses of findings from multiple independent studies than is possible at present and provide the conditions for a cumulative incremental literature on medication adherence interventions to develop.

### **3.4.9 Conclusion**

This review and meta-analysis of interventions documented significant but modest post-intervention improvements in BP outcomes among hypertensive patients. However this is a tentative finding as substantial heterogeneity and potential biases were present.

#### **4. Study 2: Behavior Change Techniques in Apps for Medication Adherence: A Content Analysis**

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##### **Abstract**

**Introduction.** There are a vast number of smartphone applications (apps) aimed at promoting medication adherence on the market; however the theory and evidence base in terms of applying established health behavior change techniques (BCTs) underpinning these apps remains unclear. This study aims to code these apps using the Behavior Change Technique Taxonomy v1 (BCTTv1; Michie et al., 2013) for the presence or absence of established BCTs.

**Methods.** The sample of apps was identified through systematic searches in both the Google Play Store and Apple App Store in February 2015. All apps which fell into the search categories were downloaded for analysis. The downloaded apps were screened with exclusion criteria and suitable apps were reviewed and coded for BCTs in March 2015. Coding was done independently by two researchers.

**Results.** In total, 166 medication adherence apps were identified and coded. The amount of BCTs contained in an app ranged from 0 -7 ( $M = 2.77$ ). A total of 12 BCTs out of a possible 96 were found to be present across apps. The most commonly included BCTs were ‘Action planning’ and ‘Prompt/cues’ which were included in 96% of apps, followed by ‘Self-monitoring’ (37%) and ‘Feedback on behavior’ (36%).

**Conclusions.** The extent to which established BCTs are used in medication adherence apps is currently limited. The development of medication adherence apps may not have benefitted from advances in the theory and practice of health behavior change.

## 4.1 Introduction

Poor adherence to medication leads to many negative health outcomes and causes approximately 33 – 69% of medication related hospitalizations. (Blaschke, Osterberg, Vrijens, & Urquhart, 2012; Osterberg & Blaschke, 2005). A recent Cochrane review found that only a minority of interventions for enhancing medication adherence were successful (Nieuwlaat et al., 2014). Mobile device applications or apps are a relatively new method with the potential to support enhanced medication adherence (Kumar et al., 2013). There is however little research or systematic evaluation of the content of the many medication adherence apps that are currently available.

An increasingly common way of analyzing the content of mobile device or ‘mHealth’ apps is to code them using a behavior change technique (BCT) taxonomy (Michie et al., 2013) or evidence based lists of specific behavior change techniques or approaches to behavioral intervention (Abroms, Lee Westmaas, Bontemps-Jones, Ramani, & Mellerson, 2013; Kumar et al., 2015; Pagoto, Schneider, Jojic, DeBiase, & Mann, 2013). BCTs are defined as the observable, replicable, components of behavior change interventions. The most recent version of a BCT taxonomy is the BCTTv1 which includes 93 distinct BCTs within 16 categories with detailed definitions of each (Michie et al., 2013). This method has been recently used to analyze apps for physical activity (Conroy et al., 2014; Middelweerd et al., 2014; Yang et al., 2015) and diet (Direito et al., 2014).

Describing the BCTs in medication adherence apps could be helpful for scientists, software developers and practitioners working in this area. Designing clearly defined and evidence-based BCTs into medication adherence apps confers a number of advantages including an increased likelihood of app efficacy to improve medication adherence, a clearer theoretical understanding of potential mechanisms of action, an increased capacity to refine and combine complementary BCTs and an enhanced ability to compare apps with similar BCT content.

Therefore the aim of the present study was to perform a content analysis of all apps for medication adherence across the Apple App Store and the Google Play Store for the presence or absence of established BCTs using the BCTTv1 (Michie et al., 2013).

## **4.2 Method**

The sample of apps was identified through systematic searches in both the Google Play Store and the Apple App Store in February 2015. Search terms were based on Boolean logic and included 'AND' combinations for medication, pill, adherence, compliance, monitor, reminder, tracker, diary and management.

All apps which fell into these search categories and fit into the inclusion criteria were downloaded for analysis. The downloaded apps were screened and coded for BCTs using the BCTTv1 in March 2015. Coding was done independently by two authors. The content and functionality of each app was examined on a mobile phone or tablet through extensive exploration of the menu options. BCTs were coded with a "0" if absent and a "1" if present. The inter-rater reliability was initially found to be moderate with Kappa = .43 ( $p < .05$ , 95% CI 0.10, 0.77). Any discrepancies in coding were related to the interpretation of the BCT within the app interface. Both reviewers went on to resolve these discrepancies with discussion and involvement of a third reviewer where necessary until consensus was reached.

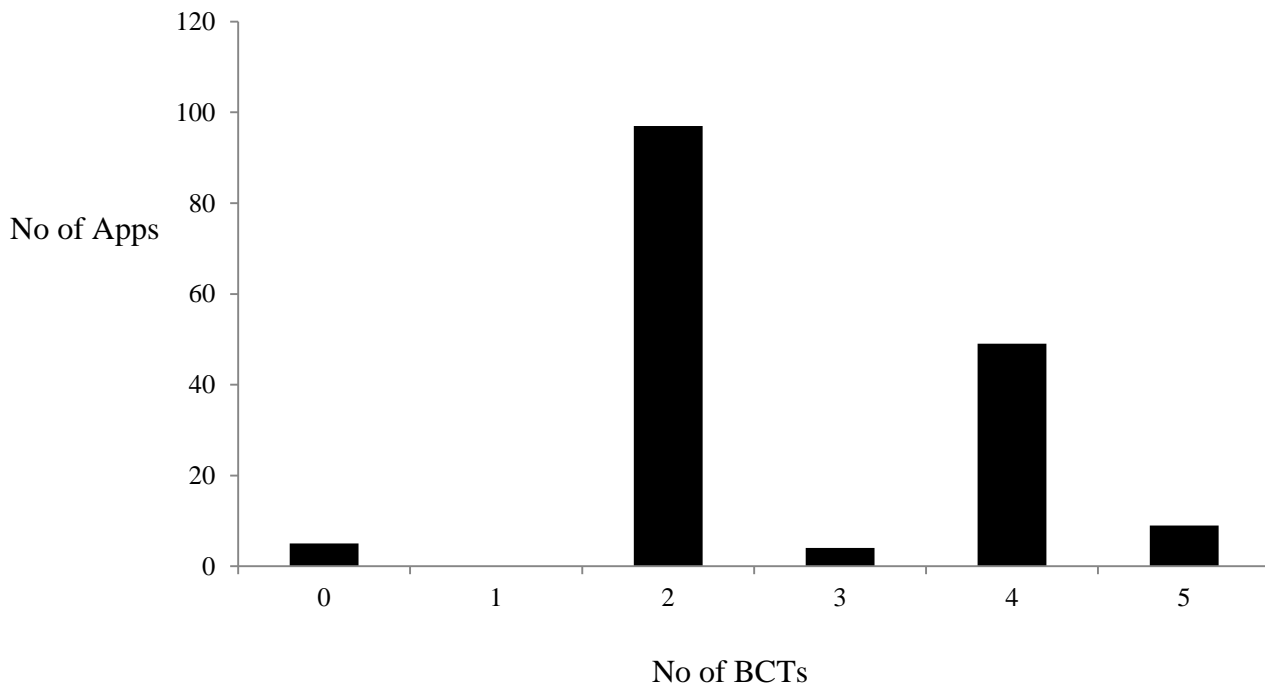
Inclusion criteria: Medication adherence as main content

Exclusion criteria: Content unrelated to medication adherence for disease management, app as a tool for an online intervention rather than stand-alone app, faulty – unable to use (e.g. crashing/freezing/downloading problems), specific to a specific country, language other than English, paid app that is no more than an advertisement free version of the free app.

Statistical analysis was conducted using IBM SPSS Statistics 20.

### 4.3 Results

A total of 1041 apps were found through systematic searching and 612 of these were unique. After screening with the exclusion criteria, 446 apps were excluded. The most common reason for exclusion (82.4%) was not having content related to medication adherence for disease management. A total of 166 apps were coded using the BCTTv1. Of these, 52 were from the Apple App Store (30 free and 22 paid) and 114 were from the Google Play Store (90 free and 24 paid). The numbers of BCTs contained in apps ranged between 0 - 7 (mean = 2.77, median = 2). See Figure 4.1.



*Figure 4.1.* Number of BCTs present in 166 apps

A total of 12 BCTs were found to be present across apps. See Table 4.1 for the prevalence of these BCTs, together with the working definition of the BCT and examples of how they were

used in the apps. Seven apps were available on both the Apple and Android platforms. Apart from slight differences in formatting, the content was the same in these.

The most common combination of BCTs within the apps was ‘1.4 Action planning’ and ‘7.1 Prompts/cues’. These BCTs were present together in 91.4% of apps. The second most common combination was ‘1.4 Action planning’, ‘2.2 Feedback on behavior’, ‘2.3 Self-monitoring of behavior’ and ‘7.1 Prompts/cues’. These four BCTs were present together in 33.9% of apps.

Table 4.1

*Prevalence of BCTs in 166 medication adherence apps*

<i>BCT</i>	<i>Definition</i>	<i>Most commonly utilized as</i>	<i>n</i>	<i>Percentage</i>
1.4 Action planning	Prompt detailed planning of performance of the behavior (must include at least one of context, frequency, duration and intensity). Context may be environmental or internal.	Setting a reminder to take medication at a specific time every day.	159	96%
7.1 Prompt/cues	Introduce or define environmental or social stimulus with the purpose of prompting or cueing the behavior. The prompt or cue would normally occur at the time or place of performance	A reminder alarm ringing to prompt the user to take medication.	159	96%
2.3 Self-monitoring	Establish a method for the person to monitor and record their behavior(s) as part of a behavior change strategy	A dialog box which allows users to record whether they took or skipped their medication.	64	39%
2.2 Feedback on behavior	Monitor and provide informative or evaluative feedback on	A log or graph which displays the user’s adherence	61	36%

	performance of the behavior	levels.		
2.1 Monitoring of behavior by others without feedback	Observe or record behavior with the person's knowledge as part of a behavior change strategy	An adherence log being sent to the user's physician at periodic intervals.	5	3%
3.1 Social support (unspecified)	Advise on, arrange or provide social support or noncontingent praise or reward for performance of the behavior.	A function to alert another person (e.g. family, care giver) when a medication dose is skipped.	4	2%
4.2 Information about the antecedents	Provide information about antecedents	A dialog box allowing users to enter and save reasons for skipping medication.	3	2%
4.1 Instruction on how to perform a behavior	Advise or agree on how to perform the behavior	Advice and pictures on how to create and use medication schedule.	1	1%
5.1 Information about the health consequences	Provide information (e.g. written, verbal, visual) about health consequences of performing the behavior	Information about the health benefits of adherence.	1	1%
6.1 Demonstration of the behavior	Provide an observable sample of the performance of the behavior, directly in person or indirectly e.g. via film, pictures, for the person to aspire to or imitate	Pictures of a completed medication schedule and video demonstration of its use.	1	1%
6.2 Social comparison	Draw attention to others' performance to allow comparison with the person's own performance	A graph comparing the user's adherence to other users with the same medical condition.	1	1%
8.1 Behavioral practice/rehearsal	Prompt practice or rehearsal of the performance of the behavior one or more times in a context or at a time when the performance may not be necessary, in order to increase habit and skill	Instruction to user to practice creating and using medication schedules.	1	1%

An independent- samples t-test was conducted to compare the number of BCTs present in free and paid apps. There was a significant difference in the number of BCTs in free ( $M = 2.64$ ,  $SD = 1.02$ ) and paid ( $M = 3.11$ ,  $SD = 1.25$ ;  $t(164) = -2.25$ ,  $p = .026$  two tailed). Both ‘2.2 Feedback on behavior’  $\chi^2(1) = 8.48$ ,  $p = .004$ , ‘2.3 Self-monitoring of behavior’  $\chi^2(1) = 13.38$ ,  $p < .001$  were more common in paid apps. Based on the odds ratio, the odds of ‘2.2 Feedback on behavior’ being present was 2.77(95% CI 1.38, 5.57) times higher in a paid app and the odds of ‘2.3 Self-monitoring of behavior’ being present were 3.64 (95% CI 1.79, 7.39) times higher in a paid app.

#### **4.4 Discussion**

The current study shows that the extent to which established BCTs are used in medication adherence apps is currently limited. This mirrors findings in other domains such as weight loss and smoking cessation (Abroms et al., 2013; Pagoto et al., 2013). The relative absence of BCTs in this context highlights an opportunity for health behavior change experts to team with software developers in developing theory-based apps with improved quality and effectiveness (Kumar et al., 2013).

The main strength of this study was the use of an established instrument (the BCTTv1) to systematically code the presence of BCTs in medication adherence apps. Unlike previous studies which tended to focus on the Apple operating system, this study also included the Android operating system. Previous research has also inclined towards coding the description of the app rather than the app itself (Abroms et al., 2013; Conroy et al., 2014). The systematic searching of apps rather than just using the top ranked apps is a methodological strength as popularity rankings in app stores are highly variable and have the potential to be easily biased by software developers with significant resources.

In terms of limitations, the usability of apps was not considered as this was beyond the scope of the current study. The results, which reflect the presence of specific BCTs in apps, do not express how these BCTs were implemented e.g. ‘2.2 Feedback on behavior’ could be present as a simple calendar log or detailed graphs of adherence. Also it has to be noted that the BCTTv1 was designed for the coding of behavior change interventions, and not for the coding of apps, and therefore some its concepts may not have fully translated for analysis of digital health behavior change interventions (Middelweerd et al., 2014). For example, it would be difficult to virtually substitute the BCT ‘12.5 Adding object to the environment’ as it requires physical objects to be added to the environment in order to facilitate performance of the behavior.

While this study provides an overview of the content of currently available medication adherence apps, future research needs to examine how BCTs can be incorporated into apps and also which particular BCTs or combinations of BCTs in an app are most effective at changing medication adherence. To accomplish this, randomized controlled trials of theory based apps are required to determine their efficacy and effectiveness (Cowan et al., 2013). There is also a need for qualitative research to investigate user experience of apps and their BCTs.

#### **4.5 Conclusion**

There are a limited number of BCTs included in contemporary medication adherence apps with most using only action planning and a prompt/cue. This research highlights the need for a link between behavior change research and software development. The findings of this study will provide valuable information for developing improved apps to enhance medication adherence.

## **5. Study 3: New self-management technologies for the treatment of hypertension: general practitioners' perspectives**

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### **Abstract**

**Background.** Digital health interventions, such as those that can be delivered via smartphone applications (apps) or wireless blood pressure monitors, offer a new, scalable and potentially cost-effective way to improve hypertension self-management. In Ireland, as is common in the UK, the majority of hypertension management occurs in general practice. Therefore, it is crucial to investigate how general practitioners (GPs) feel about and engage with the growth of these new methods of self-management of blood pressure.

**Aim.** To explore GPs' perspectives of self-management technology to support medication adherence and blood pressure control in patients with hypertension.

**Design and Setting.** This was a qualitative interview study based in the West of Ireland. Ten GPs who were purposively sampled participated in semi-structured interviews. Thematic analysis was carried out on the data.

**Results.** Three major themes were identified; current reach and future potential; empowerment; and responsibility.

**Conclusions.** GPs could see the benefit of using these technologies, such as more accurate blood pressure data and potential to engage patients in self-management. Concerns relating to

the increased workload associated with a potentially unmanageable quantity of information and an increase in healthcare use among the ‘worried well’ also emerged strongly from the data.

## **Keywords**

Hypertension, primary health care, technology, blood pressure monitors self care, qualitative research.

## **5.1 Introduction**

Interventions to enhance adherence to anti-hypertensives often involve self-monitoring of blood pressure (e.g. Hosseininasab et al., 2014; Margolius et al., 2012; Marquez-Contreras, Martell-Claros, Gil-Guillen, de la Figuera-Von Wichmann, Casado-Martinez, Martin-de Pablos, Figueras, Galera, & Serra, 2006) and contain medication reminders such as environmental prompts or cues (e.g. Morrissey et al., 2017). There is evidence to suggest that these methods have established efficacy to improve adherence (Fletcher et al., 2015; Glynn et al., 2010; Vervloet et al., 2012). Digital health interventions, such as those that can be delivered via smartphone applications (apps) or wireless blood pressure monitors, offer a new, scalable and potentially cost-effective way to improve medication taking behaviours. In the case of hypertension they may provide a feasible method of supporting reminder strategies and self-monitoring of blood pressure (Band et al., 2017). It is widely recognised that significant numbers of patients are already engaging with this type of technology, as there is sometimes more health technology available to patients in their home environment than there is provided by their general practitioners (Young, 2016).

In Ireland, as is common in the UK, the majority of hypertension management occurs in general practice. Therefore it is crucial to investigate how general practitioners (GPs) feel about and engage with the growth of these new methods of self-management of blood

pressure. While self-monitoring of blood pressure is recommended in the UK as detailed in the NICE 2011 and ESH/ESC Europe 2013 guidelines, a recent thematic synthesis on the topic (Fletcher et al., 2016) found that GPs were uncertain on how to integrate it into everyday practice as there are no clear current clinical guidelines. A recent UK qualitative study on primary care practitioners' views on the HOME BP system (an online intervention for hypertension management, including self-monitoring of blood pressure and home titration) described both primary care practitioners' benefits and concerns. They felt that this specific system could empower patients to self-manage health and potentially save both patient and primary care practitioner time but were worried about the accuracy of the data and the potential to increase health anxiety (Bradbury et al., 2017).

While much of the qualitative research to date on this topic has focused on GP's views on specific digital interventions (e.g. Bradbury et al., 2017; Hallberg et al., 2016; Jones et al., 2013; Leon, Surender, Bobrow, Muller, & Farmer, 2015), there is relatively limited data on the attitudes of GPs to this kind of technology to support hypertension medication adherence more generally. Therefore, the aim of this qualitative research is to explore GPs' perspectives of contemporary self-management technology to support medication adherence and blood pressure control in patients with hypertension.

## **5.2 Method**

The study is reported using the consolidated criteria for reporting qualitative research (COREQ) checklist (Tong, Sainsbury, & Craig, 2007) for focus groups to ensure rigor in reporting in how the study was conducted (see Table 5.1).

Table 5.1.

*The CORE-Q checklist*

<b>Item</b>	<b>Description</b>
<b>Domain 1: Research team and reflexivity</b>	
<i>Personal Characteristics</i>	
1. Inter viewer/facilitator	One author (EM) conducted the interviews
2. Credentials	BA., MSc.
3. Occupation	PhD Candidate
4. Gender	Female
5. Experience and training	Trained in qualitative methods and design, experience in conducting focus groups
<i>Relationship with participants</i>	
6. Relationship established	EM contacted participants via email or telephone to discuss arrangements for interviews. Otherwise participants had no relationship with the researcher.
7. Participant knowledge of the interviewer	Participants were informed that the researcher was conducting a PhD in the area of digital interventions for hypertension and her goal was to understand GPs perspectives on this.
8. Interviewer characteristics	The researcher was closely engaged in the research process and therefore unable to avoid personal bias. This research sought to inform the content of an intervention.
<b>Domain 2: study design</b>	
<i>Theoretical framework</i>	

9. Methodological orientation and theory	Thematic analysis was used in this study. An inductive approach was adopted
<i>Participant selection</i>	
10. Sampling	GPs in the west of Ireland were sampled purposively.
11. Method of approach	From November to December 2016, GPs were contacted by the lead researcher and asked to participate.
12. Sample size	There were 10 participants in the study.
13. Non-participation	All participants who agreed on a date and a time took part in an interview.
<i>Setting</i>	
14. Setting of data collection	Data was collected at the GPs' clinics.
15. Presence of non-participants	No non-participants were present.
16. Description of sample	Characteristics of the sample can be seen in Table 1.
<i>Data collection</i>	
17. Interview guide	The interview schedule was developed by reviewing other qualitative research in the area. It was then reviewed by the research team and piloted on one GP.
18. Repeat interviews	No repeat interviews were carried out.
19. Audio/visual recording	Audio recording was used to collect the data.
20. Field notes	Field notes were made during and after the interviews.
21. Duration	Each of the interviews lasted a minimum of 20 minutes.
22. Data saturation	The researchers decided that data saturation had been achieved after the 10 <sup>th</sup> interview. The transcripts were reviewed as soon as possible after each interview. Saturation was achieved as no further additional new information began to

emerge. It was agreed that the addition of new codes was unlikely after 10<sup>th</sup> interview.

23. Transcripts returned

Transcripts were not returned to participants for comment and/or correction.

### **Domain 3: analysis and findings**

#### *Data analysis*

24. Number of data coders

Two data coders (EM and MC) coded the data

25. Description of the coding tree

Open coding was firstly performed. This consisted of transcripts being read thoroughly and sections of text being assigned to descriptive codes. Content of the transcripts was constantly compared to codes that were already established. After forming the codes, they were grouped into categories, which were then grouped into themes.

26. Derivation of themes

All five members of the research team came together to review all the data and contribute to the thematic analysis.

27. Software

Data was managed using NVivo 11.

28. Participant checking

Participants did not provide feedback on the findings.

#### *Reporting*

29. Quotations presented

Participant quotations are presented to illustrate the themes/findings. Each quotation is identified using the participants' age and gender.

30. Data and findings consistent

There is consistency between the data presented and the findings. The unit of analyses was the theme rather than the prevalence or frequency of statements. Some statements of quantification are included (e.g., statements such as often, sometimes), but do not always aim to provide estimates of prevalence.

31. Clarity of major themes

Codes identified in the open coding stage were discussed by two study authors until consensus was reached. All major themes clearly presented in the findings.

32. Clarity of minor themes

There is a description of sub themes in the findings.

### **5.2.1 Recruitment**

GPs from the west of Ireland were recruited purposively based on age, gender, years of practice, practice size and practice location (urban/rural). Ten interviews were conducted in total. See Table 1 for characteristics of participants. In order to be responsive to, and incorporate findings from the data as they emerged, an iterative approach was used (Ziebland & McPherson, 2006). As is common in qualitative sampling methodology recruitment continued until data saturation was reached and no new themes emerged (Glaser et al., 1968).

### **5.2.2 Interviews**

The interview topic guide was developed by reviewing other qualitative research in the area. This topic guide was then reviewed by the research team and piloted on one GP. This led to the final topic guide (See Appendix X). When asking GPs about contemporary self-management technologies, the interviewer described a typical hypertension management smartphone app that would be seen on the global app market. These tend to consist of two parts – the first is a reminder to take medication, the second is home BP monitoring where the patient has a home BP monitor which is connected to the app via Bluetooth. The monitor sends the BP values to the app and produces a graph of BP measurements. The interviews were semi-structured and carried out by one researcher (EM) who travelled to the GPs' clinics. The participants individually consented to the interviews being conducted and recorded and to anonymous quotations being used. Transcription was conducted by the research team as it has been argued that transcription helps the interpretive process and should be seen as the first step in the process of data analysis (Bailey, 2008).

### 5.2.3 Analysis

The five stage of thematic analysis (familiarisation, generation of codes, searching for themes, reviewing themes and defining themes) (Braun & Clarke, 2006) were followed. Coding was partially conducted with another researcher (MC) from a different professional background (nursing) to the main investigator (psychology) for inter-coder reliability (Pope et al., 2000). To heighten reflexivity, four members of the research team (two health psychologists, a GP and a nurse) joined the lead researcher (PhD candidate in health psychology) to review all the data and contribute to the thematic analysis (Richards, 2014). NVivo (version 11) was used to organise and code the transcripts to facilitate the analysis and comparison of relationships between codes (Pitney & Parker, 2009).

### 5.3 Results

Participant characteristics are shown in Table 5.2. Three main themes were identified in the data: current reach and future potential; empowerment; and responsibility.

Table 5.2.

*Characteristics of interviewed GPs, n = 10*

Characteristic	
Mean age, years (range)	45 (34-72)
Female, n (%)	3 (30)
Urban, n (%)	4 (40)
Practice size, patients (range)	4110 (1500-10000)
Mean years of practice (range)	16 (2-43)

### 5.3.1 Current reach and future potential

The first theme that was generated was current reach and future potential. This refers to the GPs' understanding of who is currently using this type of technology to manage hypertension and who might be suitable candidates to target for this type of intervention either now or in the future.

GPs were aware that a lot of the public are already very engaged with technology in general, particularly the younger generation. They anticipated that these patients could be using smartphones for health reasons, as they were already using them for managing many other parts of their lives.

*'I suppose people are so dependent on their phones now and they're using them for so much, I certainly think that if not now, over the next ten years, that 30 year old crowd, that 30, 40 year old generation now would be moving on. And certainly they're a group that would certainly be using their phones; you could say day in, day out but it's even minute in, minute out, you see it with some people. I suppose personally like, my banking, I'm doing that off my mobile and my shopping, I'm doing that off my mobile.'* [Female, 35]

They also recognised that technology is rapidly growing and there is a need to come to terms with that. They expressed an awareness of how common using technology to manage chronic conditions could be in the future as smartphone penetration grows.

*'I think it's ridiculous to think that they won't become more prevalent and more used across numerous conditions as time goes on.'* [Male, 37]

They were readily able to identify patients who they thought would be willing to engage with technology to manage their hypertension.

*'Some people, the young hypertensives who are managing their medication amongst lots of other things, young kids, business whatever, superb, they're already efficient you know, if you want something done ask a busy person. Those people would appreciate that vehicle for keeping their BP down.'* [Male, 43]

These patients tended to be younger, technology-savvy and motivated about their healthcare. While GPs did think that using technology was a good choice for these types of patients, they expressed concerns about the patients' motivations. One concern was that the only type of patient who would use technology would already be highly motivated about their health, and would not necessarily need the extra facilitation that such technology would provide.

*'And the other thing is I would say that patients that will use the apps would probably be compliant anyway!'* [Female, 33]

Some also felt that this technology, while having potential to be useful could actually have relatively limited impact as it wouldn't reach the people who need it most, whether it was through their lack of motivation or their circumstances. One GP outlined a particular situation where he felt this was the case.

*'I would be slightly concerned that the people who are most likely to use the app are the least likely to forget their medication in the first. I mean, in particular patients, I'm just thinking of one patient in particular who is high risk with high BP, she's had a subarachnoid already so BP is crucial that it's monitored. She has impaired glucose as well, impaired kidney function but socially it's a disaster what's going on at home. So I just don't see that those apps are going to be a help to her who is probably the type of patient who we most want to help. So I think they're definitely going to have a role, but are they going to have a role for those patients who are most likely to benefit, I'm not sure.'* [Male, 50]

As well as being unsure if this technology would reach the right patient, GPs also stated concerns about technology reaching the wrong patient. Several talked about the risk of home blood pressure monitoring leading to unnecessary anxiety in patients.

*'They can bring problems and particularly anxious people; it can really feed into their anxiety. That really can be a problem. And you know, can start a cycle of phone calls in the middle of the night.'* [Female, 37]

### **5.3.2 Empowerment**

The second theme that was identified was empowerment. GPs spoke about how patients using this kind of technology could empower their practice. The unreliable nature of office blood pressure readings was mentioned across all interviews. Many of the GPs quickly acknowledged that using technology to monitor and store blood pressure readings over time would enable them make more accurate clinical judgements.

*"Yeah well any time I sit down with a hypertensive patient, I'm conscious of the fact that whenever I take their BP as a spot reading in the office, it's often hopelessly inaccurate. So anything we can do to make better clinical decisions around that I think we should welcome."* [Male, 44]

They also recognised that having this data around blood pressure measurements would make some conversations with the patient easier. Several GPs spoke about how difficult it is to explain to consequences of high blood pressure and the need for anti-hypertensives, particularly when the patient doesn't feel ill. They thought that having a visualisation of the effect of anti-hypertensives on the patients' blood pressure would be a useful aid in explaining this.

*“Because often times if you speak of long term risks and benefit, that doesn’t necessarily ring true to the patient as much as seeing a graph and being able to track it themselves.” [Female, 33]*

They also talked about this visualisation of blood pressure readings could empower the patient. Many felt that by being able to see a reduction in blood pressure, patients would be more motivated to change their lifestyles or keep adhering to their medication.

*“If you have an app that will enable you to keep a record, and again that added action of recording and inputting means that the patients probably buy in a bit more. So you would expect that their compliance would be a lot better if that was the case because they feel more involved and that they have ownership of it.” [Male, 37]*

However, this empowerment of the patient was not always seen as a positive thing. One GP spoke about how some of her patients who regularly use an app for adherence to the contraceptive pill take the more senior role in their conversations – the opposite of the traditional doctor-patient relationship.

*“I mean lot of the ones that they’re using in terms of contraception, they’re showing me what they’re using, I wouldn’t be advising on any of those – it’s the other way around.” [Female, 35]*

This disruption of the power dynamic within the consultation lead to a certain amount of concern in GPs, as they were worried that patients were not appropriately educated and could be accessing and acting on incorrect information.

*“Patients are using technology and accessing information and it’s not necessarily always the right information. I mean I have websites that I get information from or recommend to patients because so many people are coming and I think our workload is*

*increasing because of people's access to information that isn't necessarily correct, the Dr. Google effort, it can be awful.*" [Female, 35]

They were aware that technology is becoming increasingly common and seemed to recognise that they may not be the only source of information and advice for a patient.

*"Overall what I think is happening is that the public are accelerating well ahead of where we as a service are."* [Male, 50]

### **5.3.3 Responsibility**

The final theme identified was responsibility. GPs had various thoughts and concerns about how responsibility of the patient's health would be managed when using technology. They felt that they would have to know a lot about an app before they would be happy to recommend it to a patient. They were also very aware, that as the authority figure, that they would need to check all aspects of an app before they can recommend it to patients.

*"Sure, about the app I'd need to know, who was behind it and who's making all the money. These are key points in medicine – who is making the money and where is the money going. And what is their motivation for targeting the patient group. You'd have to have clearly seen the insides and outsides of the app and you'd want to want to be very guarded against pharma agendas, loaded into apps...suggesting drugs.. You'd also need to be very aware of incorrect advice, incorrect information being provided in the apps."* [Male, 38]

In terms of division of responsibility between the doctor and the patient, opinion differed depending on the type of technology. When considering patients using a digital reminder to help them to remember to take their medication, GPs were happy to encourage this, as it was the patients' own responsibility.

*“Yeah, I’ve no problem with it, you set it and you get reminders, people do it for pills all the time, put alarms on to remember it in the morning. Yeah so I’ve no problem with digital reminders or whatever.”* [Male, 38]

However, when reflecting on patients using home blood pressure monitors where the readings could be sent directly to the GPs’ offices, the perspectives were more complex. They were concerned about what this meant for their duty of care. Several talked about how it was already difficult to define where duty of care begins and ends. They feared that technology may amplify this concern as it created the potential for the beginning and end of duty of care to change and possibly expand. There was an immediate worry about receiving blood pressure measurements and not being able to act on them.

*“There are issues with information being sent in outside of office hours, and responsibility if there are acute or urgent BP measurements. So you might have something that needs action and needs to be acted on and then if you’re not able to get in contact with that person...”* [Male, 37]

The overworked state of primary care in Ireland was also mentioned – although there was some dissonance on the role technology played in this. Some felt that as GPs are quite overburdened and under resourced that this technology could move responsibility to patient for their own care which would be helpful.

*“Everyone agrees that the current, and it’s not just Ireland, its everywhere, that the current healthcare systems are struggling with capacity so the more that patients can do, I think the better as an overall principle”* [Male, 50]

Other respondents indicated that more responsibility would be shifted onto them rather than the patient. They spoke about how the difficulties of taking this responsibility on and how it

may have limited applicability to the current context and culture of general practice in Ireland.

*“I think we’re going to be slow to adopt them as GPs but that’s a complete fear around increased workload. You can’t be crying poor all the time but you can’t comprehend anything that’s going to add to your workload that isn’t necessarily going to have clear outcomes, clear improvement outcomes”* [Female, 37]

## **5.4 Discussion**

### **5.4.1 Summary**

The data from these interviews provide valuable insights into GPs’ perspectives on using contemporary self-management technology to support the management of hypertension in the community. Three major themes were identified. These were current reach and future potential; empowerment; and responsibility. Overall GPs could see the benefit in using these technologies, such as more accurate blood pressure data and potential to engage patients in self-management, but this was weighed against their concerns. Concerns primarily centred on increased workload as GPs feared having to manage large amounts of data and were concerned about who was responsible for this data. In addition, there was the potential for, in some cases, increased healthcare use among those with health anxiety i.e. the ‘worried well’ phenomenon. Potential disruption of the traditional doctor-patient relationship also emerged as a significant concern.

### **5.4.2 Strengths and limitations**

This study provides novel and timely data on GPs’ perspectives of using contemporary self-management technology to support the management of patients with hypertension. While the number of GP participants was lower than some related studies on this topic, the sampling

methodology was determined *a priori* and the 10 interviews achieved data saturation. Additionally, one--on-one interviewing allowed GPs to express their individual opinions without the social desirability biases that might pertain in focus groups or other group based methods of data collection. Reflexivity was increased by the multidisciplinary research team coming together to review the data, however it is possible to also view this as a limitation as the team may have taken a different emphasis from that of an independent observer. Another obvious limitation of the work is that the views of this relatively small sample from one geographical location may not comprehensively capture the perspectives of GPs as a whole, however the consistency of the data with findings from other contexts (Bradbury et al., 2017; Morton et al., 2016) suggest that these findings have external validity. It may also have been of benefit to include practice nurses as they also typically constitute part of the primary care team, therefore we acknowledge that these data have not captured the full primary care team's perspective.

#### **5.4.3 Comparison with existing literature**

The findings of this study support previous reviews of the research in the field of using self-management technology to manage chronic conditions in general. A recent meta-ethnography of digital interventions for self-management of chronic physical health conditions by Morton et al. (2016) concluded that health care professionals were less positive about using technology than patients were, as they had concerns about the increased workload. Increased workload in primary care in both the UK and Ireland has become a major concern in recent years. Crosson, Ashdown, and Hobbs (2017) report that GPs in England describe their working days as being long and intense, leading to worries over the wellbeing of GPs and their ability to provide high quality care to their patients. As with the current study, the

evidence from this review of qualitative research suggested that health care professionals' concerns around technology were at least as strong as the perceived clinical benefits.

A recent meta-synthesis (Mudge, Kayes, & McPherson, 2015) on clinician's role in self-management approaches, including technology, reported that clinicians can find sharing control of the condition management with the patient to be challenging. This was observed in the current study under the emergent theme of "empowerment". Mudge et al. (2015) report that some specific skills such as; practicing reciprocity in communication style, peer support and self-reflection were helpful in shifting clinician's ways of practice from a paternalistic to a more collaborative approach. It is possible that these strategies may also be helpful for GPs as the use of these technologies grows.

In terms of hypertension, Bradbury et al. (2017) conducted a similar qualitative study with health care professionals and the HOME BP online system. They also found that health care professionals were concerned about increasing patient anxiety. However the authors note that in previous research on home blood pressure monitoring (e.g. Jones et al., 2013; McManus et al., 2010) evidence has emerged that patients do not exhibit increases in anxiety while measuring blood pressure at home.

In fact, it has already been shown that technology has the potential to trigger a complex yet engaging behavioural change process for patients for the management of hypertension, hence enabling individuals to take ownership of their own health and healthcare at a time and place of their own choosing (Glynn et al., 2015). As it will not be possible to turn back the clock on such technological advancement, it would seem the only decision to be made by health care professionals will be how they will engage with this process of change.

#### **5.4.4 Implications for research and practice**

Newer technologies such as mobile information and communication devices and the internet have been embraced across the globe despite technological challenges and concerns regarding privacy and security. In the design and development of technology based self-management tools for the treatment of hypertension, flexibility and security are vital to allow and encourage patients to customise, personalise and engage with their devices (Glynn et al., 2015).

This study has clearly recognised that patients' use of technology may have the potential to increase the amount of blood pressure data available to health care professionals. Provided the quality of this data is assured, then it will enable health care professionals to make better clinical decisions in the management of hypertension. This more collaborative approach in patient care could also facilitate greater awareness and increased self-management by patients themselves.

The reluctance of health care professionals to engage with newer technologies is evident from the data in this study. This reticence is likely to change if the emergence of newer technologies was accompanied by the emergence of an evidence base demonstrating effectiveness and cost-effectiveness. In addition, health regulation bodies may also have a role in quality control and the provision of explicit guidelines in relation to such interventions. Examples of this that already exist are the NHS Health Apps library in the UK which provides patients with access to a list of recognised and endorsed health apps.

Overall GPs could see the benefit in using technology, such as more accurate blood pressure data and potential to engage patients in self-management, but this currently seems to be outweighed by their concerns. Concerns primarily centred on increased workload as GPs

feared that more blood pressure data would lead to more responsibility for an unmanageable quantity of information and an increase in healthcare use among the ‘worried well’.

## **6. Study 4: Smartphone apps for improving medication adherence in hypertension: patients' perspectives**

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### **Abstract**

**Purpose:** Digital interventions, such as smartphones apps, are becoming an increasingly common way to support medication adherence and self-management in chronic conditions. It is important to investigate how patients feel about and engage with these technologies. The aim of this study was to explore patients' perspectives on smartphones apps to improve medication adherence in hypertension.

**Patients and Methods:** This was a qualitative study based in the West of Ireland. Twenty four patients with hypertension were purposively sampled and engaged in focus groups. Thematic analysis was carried out on the data.

**Results:** Participants ranged in age from 50 to 83 ( $M = 65$  years) with an equal split between males and females. Three major themes were identified in relation to patients' perspectives on smartphones apps to improve medication adherence in hypertension. These were 'development of digital competence', 'rules of engagement' and 'sustainability' of these technologies.

**Conclusion:** These data show that patients can identify the benefits of a medication reminder and recognise that self-monitoring their BP could be empowering in terms of their understanding of the condition and in interactions with their GPs. However, the data also

revealed that there are concerns around increasing health-related anxiety and doubts about the sustainability of this technology over time. This suggests that the current patient perspective of smartphone apps might be best characterized by ‘ambivalence’.

**Keywords:** Qualitative, high blood pressure, digital technology, self-management

## 6.1 Introduction

Hypertension is an important risk factor for cardiovascular and cerebrovascular events (Kearney et al., 2005). It is estimated that hypertension currently affects one billion people worldwide (Alwan, 2011) and this number is expected to increase with population growth and aging. Therefore, this condition represents a global health challenge (Forouzanfar et al., 2017).

Blood pressure (BP) control through pharmacological treatment has led to substantial benefits in the prevention of morbidity and mortality from cardiovascular disease (Wright & Musini, 2009). A Cochrane review by Musini et al. (2009) conducted an assessment of all the trials of blood pressure lowering therapy in people with hypertension aged 60 years and over and found that these treatments reduced death, strokes and heart attack. However, despite the efficacy of anti-hypertensive agents, there is a significant problem of non-adherence to these medications in those diagnosed with hypertension (Durand et al., 2017; Vrijens et al., 2017); therefore the effectiveness of current treatment is limited.

As a largely asymptomatic disease, hypertension presents a challenge for appropriate adherence to treatment and engagement with self-care (Holt et al., 2014). High adherence (defined as medication possession ratio of 80 % to 100%) to hypertensive medications is associated with higher probability of blood pressure control compared with those with medium or low levels of adherence (Bramley et al., 2006). Evidence from a number of studies suggests that as many as 50% to 80% of patients prescribed pharmacological

antihypertensive therapy have low adherence to their treatment regimen (Elliott, 2008) and this may be most important cause of failure to achieve BP control (Sabaté, 2003).

Interventions to enhance adherence to anti-hypertensives often involve self-monitoring of blood pressure (e.g. Hosseininasab et al., 2014; Margolius et al., 2012; Marquez-Contreras, Martell-Claros, Gil-Guillen, de la Figuera-Von Wichmann, Casado-Martinez, Martin-de Pablos, Figueras, Galera, Serra, et al., 2006) and contain medication reminders such as environmental prompts or cues (Morrissey et al., 2017). There is evidence to suggest that these methods have established efficacy to improve adherence (Fletcher et al., 2015; Glynn et al., 2010; Patel et al., 2013). Digital health interventions, such as those that can be delivered via smartphone applications (apps) or connected wireless blood pressure monitors, offer a new, scalable and potentially cost-effective way to improve medication taking behaviors. In the case of hypertension, they may provide a feasible method of supporting reminder strategies and self-monitoring of blood pressure (Band et al., 2017), without overwhelming capacity within the healthcare system. However uncertainties about the appropriate implementation of these technologies remain among clinicians involved in the management of hypertension (Morrissey, Glynn, Casey, Walsh, & Molloy, 2017).

A content analysis by Kumar et al. (2015), focused on apps for hypertension management, found that as well as containing tools for specifically for medication adherence (e.g. pill reminders) these apps typically also contained a BP tracking function through a wireless BP monitor. Green (2015) claims that the emergence of these types of smartphone apps offer a new important strategy for patients and their families to be more actively involved in hypertension self-care. While these technologies may have the potential to support the clinical and self-management of hypertension, there is also significant theory and evidence indicating that new tasks and technologies have the potential to create an undesirable burden (May et al., 2014) for people with these conditions and it remains unclear whether these

technologies are feasible, acceptable and usable in the context of self-management of hypertension (Hallberg et al., 2016). Therefore, it is useful to investigate how patients themselves feel about and engage with these types of apps in the context of one of the most common health conditions of older adulthood. The aim of this study was to explore patients' perspectives on smartphones apps to improve medication adherence in hypertension.

## **6.2 Method**

### **6.2.1 Design**

A qualitative descriptive study was conducted. Discussion in the focus groups centered on usability and acceptability of an app to self-manage hypertension, as participants interacted with the app for the first time during the focus group. The study is reported using the consolidated criteria for reporting qualitative research (COREQ) checklist (Tong et al., 2007) to ensure rigour in reporting how the study was conducted (see Appendix XIV).

### **6.2.2 Sample and Recruitment**

Participants for the focus groups were recruited through Croí, a heart and stroke charity based in the West of Ireland, who advertised it through email and social media channels.

Hypertensive patients who were prescribed at least one anti-hypertensive medication were eligible to take part. Participants were sampled purposively to ensure adequate variation in age, sex, length of hypertension diagnosis and anti-hypertensive prescription and experience with technology. Eight focus groups were held with 24 participants. All participants provided written informed consent and received a €20 voucher for their participation.

In order to be responsive to, and incorporate findings from the data as they emerged, an iterative approach was used (Ziebland & McPherson, 2006). As is common in qualitative sampling methodology recruitment continued until data saturation was reached and no new

themes emerged (Glaser et al., 1968). The focus groups were conducted in Croí House, the charities dedicated heart and stroke center.

Table 6.1.

*Participant characteristics, n = 27*

Characteristic	
Mean age, years (range)	64 (49 – 83)
Gender	
Male	13
Female	14
Education-Highest level achieved	
Primary	
Secondary	12
Third level	15
Employment	
Full time	7
Part time	5
Retired	15
Marital status	
Married	20
Single	7
Location	
Urban	16
Rural	11
Health insurance (%)	75%
Mean length of time since diagnosis, years (range)	12 (1-39)
Mean length of time since anti-hypertensive prescription,	11 (1-35)

years (range)

Mean amount of anti-hypertensive medications, n (range) 2 (1-4)

Mean amount of other medications, n (range) 1 (0-5)

Smartphone user (%) 70%

Health App user (%) 11%

Mean MMAS score, n (range) 1 (0-4)

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### 6.2.3 The App

MiBP is a smartphone app for hypertension self-management. It is typical of current hypertension self-management apps in that it consists of two main aspects – the first is a reminder to take medication, the second is home BP monitoring where the patient has a home BP monitor which is connected to the app via Bluetooth. The monitor sends the BP values to the app and produces a graph of BP measurements. See Figure 6.1 for screenshots of the app.

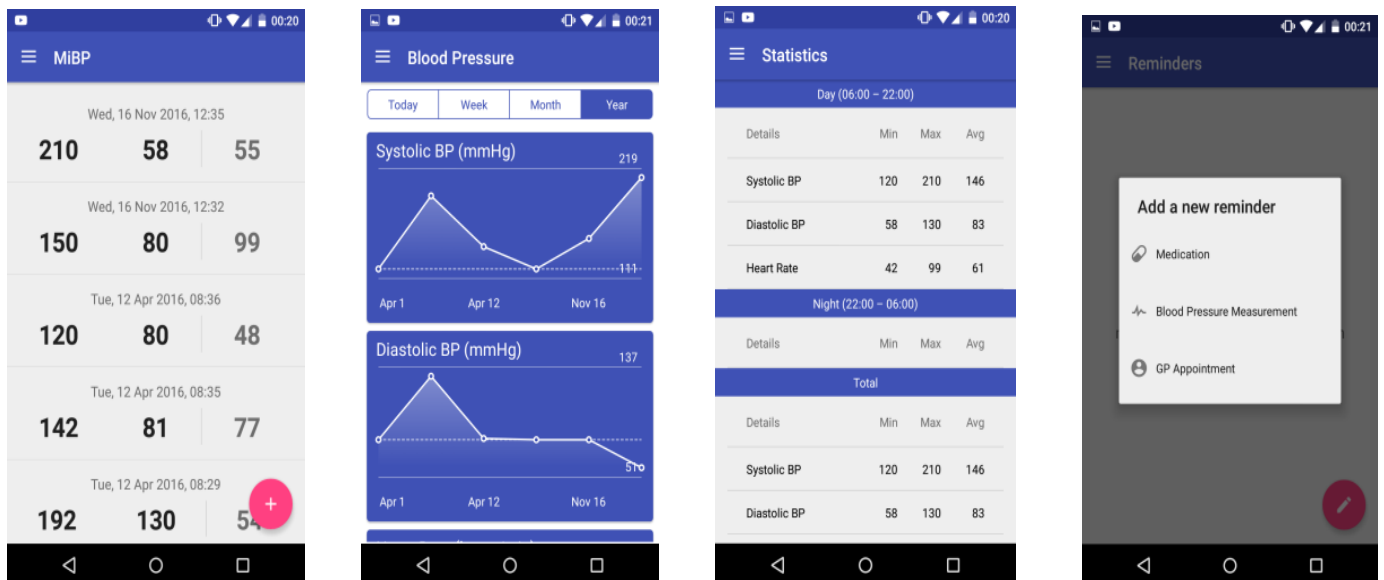


Figure 6.1. Screenshots of MiBP

#### **6.2.4 Data Collection**

Eight focus groups were conducted in total. The focus groups ranged between 3 and 5 per group. The topic guide was developed by reviewing other qualitative research in the area and subsequently revised by the research team and piloted with two hypertensive patients. This led to the final topic guide. The participants individually consented to the focus groups being conducted and recorded and to anonymous quotations being used

#### **6.2.5 Data Analysis**

The five stage of thematic analysis (familiarization, generation of codes, searching for themes, reviewing themes and defining themes) (Braun & Clarke, 2006) were followed. Coding was partially conducted with another researcher (MC) from a different professional background (nursing) to the main investigator (psychology) for inter-coder reliability (Pope et al., 2000). To heighten reflexivity, four members of the research team (two health psychologists, a GP and a nurse) joined the lead researcher (PhD candidate in health psychology) to review all the data and contribute to the thematic analysis (Richards, 2014). NVivo (version 11) was used to organize and code the transcripts to facilitate the analysis and comparison of relationships between codes (Pitney & Parker, 2009).

#### **6.2.6 Ethical Approval**

Ethical approval for this study was sought and obtained from Galway University Hospitals Clinical Research Ethics Committee.

### **6.3 Results**

Participant characteristics are shown in Table 6.1. Three main themes were identified in the data: development of digital competence, rules of engagement, and sustainability and maintenance.

### 6.3.1 Development of digital competence

The theme of “development of digital competence” refers to the pathway to becoming familiar and comfortable with using technology to manage hypertension. Participants varied in the extent to which they had developed (or desired to develop) digital competence. This ranged from not having any interest in engaging with the technology, to be fully competent and confident in its use.

Several participants said that they were not interested in using a smartphone app for hypertension management and had no desire to become digitally competent. Many of them felt that they had adequate systems already in place – both to monitor their BP levels and remember to take their medication.

*‘I wouldn't see myself using it [the app] at the moment. At the moment I have an old notebook beside the what not [BP monitor] and if I think I need to record something I'll stick it into it and then if I'm looking for a trend I'll just scan down the notebook’*

- Focus Group 3, Male (65)

*‘I just think it's like everything, it becomes a habit. I don't think you need a piece of technology to remind you to take a tablet because if you are taking... I mean do you need technology to remind you to have breakfast or brush your teeth or have a shower? The answer is no. I think if you are used to doing this as part of a routine I just think in general it just all fits in together.’*

- Focus Group 5, Female (66)

Others felt that while many of their current systems were not perfect, using the medication reminder function of the app would mean that they were “giving in” to technology. One participant outlined how this discomfort was preventing him from engaging with the app.

*'I'm kind of afraid in a way to use it because I kind of look at that maybe I might be admitting that the memory isn't as good as it used to be...I kind of like to think that I'd have no problem, I'll remember it, I will remember this or to do it...'*

- Focus Group 5, Male (50)

While some of these patients were sure that they would never use the app, others felt while they were not currently interested, that they might use it in the future. They could see the benefit of the app in supporting their hypertension self-management but did not identify as being hypertensive enough to currently need it.

*'When I saw it I thought that I'd never use it and I think now after listening to everybody discussing things I'm probably very lucky that I'm on mild medication and I thought well if I was in the severe end of the spectrum it would be excellent to have. Maybe if I disimproved or something like that I could definitely see or if I ended up living on my own which hopefully is not going to be likely.'*

- Focus Group 1, Female (61)

Further along the pathway to digital competence were those who were interested in using the app, but did not feel comfortable with operating a smartphone to the level required. A need for instruction and practice was expressed by several participants.

*'It's good but you'd need it to be explained. I think initially if you get one lesson. If it's explained to you and if you could get one follow up I think I would use it then.'*

- Focus Group 2, Female (82)

Some participants valued the outputs of the app, such as graphs of BP readings, and cited these as a motivation to become familiar with the technology. They felt empowered by this

data and felt that this was an encouragement to continue using the app and become familiar with the different functions.

*Participant 1: Using it [the app] gives you great confidence.*

*Participant 2: It would because it's your own health and there's nothing more important.*

*Participant 3: Yeah, it makes you feel good.*

- Focus Group 2, Female (65), Female (82), Female (65)

### **6.3.2 Rules of engagement**

The second theme was rules of engagement. This centered on participants engagement and disengagement with the different functions of the app, and their motivations to do so.

Very few of the participants had been using a smartphone app to manage their hypertension before this study. Most of these were not engaging with this type of technology because they were not aware of it. Lack of knowledge around apps for hypertension management was frequently spoken about in the focus groups.

For those who were already using a BP monitor at home there were very mixed opinions about the amount of time someone should spend measuring and monitoring BP. This dissonance was seen in some participants who were extremely engaged, and those who were less interested. None of the participants expressed any knowledge of the official recommendations for home BP monitoring.

*'Yeah, I bought a machine straight away. I was testing myself three times a day and before I'd see the consultant. I'd check myself three times a day and then I'd give him an excel sheet with all my readings on it. I'm too young like.'*

- Focus Group 1, Male (65)

*'Sometimes I'd use the monitor at home... It holds I think maybe 15 in memory but I never bother with the memory. If I'm hitting my target range, forget about it. If I'm outside the target range, take it again tomorrow and see if there's something.'*

- Focus Group 7, Male (61)

Some participants expressed a reluctance to engage with the home BP monitor aspect of the app. There was a sense of ambiguity around what to do with the readings, particularly if they were high. This led some participants to consider it to be unnecessarily anxiety provoking, and possibly leading to needless concern and doctor visits.

*'I think it could make you a hypochondriac at times. That something could be wrong and you go running off to the doctor...'*

- Focus Group 3, Female (71)

However, for others, the home BP monitor aspect of the app was a big motivation for engagement. Some participants really liked the idea of having their BP reading presented visually, and were particularly impressed being able to view a graph of their BP readings over time.

*'The presentation gives you a constant read and you can always check back without... Just to see how things are. You could look back at what it was and you can see between November and February how you were getting on and you get a fair idea that overall you have been very well balanced for the last three or four months.'*

- Focus Group 7, Male (83)

As well as feeling empowered by being able to follow and track their BP readings, participants also felt that the app could empower them when visiting a doctor.

*'The big advantage I have with this app is when I go to the consultant I can hand him the phone... Because I know with the consultant the minute I walk out the door he's forgotten I was there and there's somebody else in after me and the poor man, he's only human he can only remember so much or whatever, he looks at the file and tries to... But I know that I go in in a year or six months later he has to say, Who's your man again? Whereas when I give him the information there and say, that's how I've been doing for the last month for example. It doesn't lie and as I said I'm feeling I'm getting more value for my money basically because you are not getting... You are not getting the thing the thing they talk about, this White Coat Hypertension because you are taking it at home on your kitchen table.'*

- Focus Group 1, Male (65)

This feeling of gaining some control over their health and healthcare drove enthusiasm for engagement with the app. The reminder aspect also featured as a motivation, particularly for participants who sometimes were out of routine.

*'I think it would be good for me because since I'm a paramedic. After I get off working 12 hours at night that's the last thing on my mind is kind of taking medication, I'm just looking for a bed to be honest. So it would be very helpful.'*

- Focus Group 5, Male (53)

*'It's more the reminder for me and to remind me not to leave them behind me because I have two daughters living in different parts of the country so when I go to them I sometimes leave the medication in an area and then I could come back without it easily enough so if I*

*had the reminder at ten I'd take the tablets and I'd put them away then. Put them into my bag or whatever.'*

- Focus Group 6, Female (65)

### **6.3.3. Sustainability**

The final theme of sustainability refers to the participants' thoughts and feelings about maintaining both hypertension self-management and use of the app in the long term.

Some participants were not comfortable with using the app in the long term without their doctors' approval. They felt that in order to keep engaging with the app, their doctor would also have to be involved. The app forming part of their doctor-patient relationship encouraged sustainability.

*Participant 1: There is another question, would it be acceptable to your doctor when you'd go in and to have your blood pressure taken and you introduced your app? Would he be okay with that?*

*Participant 2: I suppose that depends on the doctor. Some of the older doctors may not be.*

*Moderator: So do you think if you went to the doctor's office and they thought the app was a good idea, would you keep using it then?*

*Participant 1: Oh yes.*

*Participant 2: Yes. Then I'd have no problem.*

- Focus Group 4, Male (79), Male (78)

Similarly, some liked the idea of the app being expanded to include the patients' medical history. They felt that this would be an advantage in any situation that required medical care and would be a good incentive to keep using it.

*'Overall I found it interesting. Like I said once if it can be expanded to include the patient's history in case of emergency or where it would be recognised in a hospital as the voice where one's personal medical history would be on.'*

- Focus Group 4, Male (79)

Others raised concerns about data regulations. One participant felt that in order to store his personal medical or BP information on an app over a period of time, he would need to know more about what kind of privacy standards the app was complying with.

*'I'd probably use the blood pressure monitoring part but there would have to be better stringent kind of regulations and I'd want to be made aware of them.'*

- Focus Group 6, Male (57)

A strong barrier to sustainability was the home BP monitoring equipment that is required to use the app correctly. Some thought that the cost of buying the equipment was too high and others felt that having to carry extra equipment around was too awkward and wasn't worth the inconvenience.

*'I just think like not everybody who has the App would want to invest in buying a blood pressure monitor...'*

- Focus Group 8, Female (64)

A common fear that was expressed was that constant reminders from the app would become annoying over time, leading to disengagement. Some participants had experienced this in the

past with other health apps. This “nagging” had lead several participants to discontinue use or delete the app.

*‘I have downloaded the BBC health programme but it was nagging me so much particularly in the evenings. For the last year I couldn't do anything with the knee so I said, I'm getting tired of being nagged so I haven't used it much.’*

- Focus Group 6, Male (50)

Finally, participants felt that this app would be very sustainable in the future. They spoke of how the younger generations are using smartphone apps for many different purposes and so would be happy to use an app for hypertension self-management in the long-term.

*Participant 2: It's the same thing basically but this is just using technology and I suppose going forward... My mother wouldn't be able to use this because she didn't grow up with it but I can see my own kids in their 30's, the first thing they go to if you ask them, Is it going to rain tomorrow, The first thing they go to is the phone*

*Participant 1: They don't buy the paper anymore they just look at the phone*

*Participant 2: So in 15 years time people will want this there's no doubt about it or anything similar. It's good.*

- Focus Group 1, Male (65), Female (61)

## **6.4 Discussion**

### **6.4.1 Summary**

The data from these focus groups provide valuable insights into hypertensive patients’ perspectives on using smartphone apps to manage hypertension. Three major themes were identified. These were ‘development of digital competence’, ‘rules of engagement’ and

‘sustainability’. Participants were at varying stages of digital competence – from having no interest in using technology to help with their self-management of hypertension to being extremely confident with the use of these kinds of smartphone apps. In those who were engaging with these apps, there was a dissonance in attitudes. Some were extremely motivated and felt empowered by the additional health data that the app was providing, whereas others expressed strong concerns about this data leading to increases in health anxiety. In terms of sustainability, some concerns were raised about using these types of apps in the long term but this was offset by a confidence that the younger generations would be very likely to engage with them fully in the future.

#### **6.4.2 Comparison with existing literature**

The findings of this study support previous research in the field of using self-management technology, such as smartphone apps, to manage hypertension. A similar qualitative study (Hallberg, Ranerup, & Kjellgren, 2016) on a mobile phone based system to support the management of hypertension found that some of the participants had difficulties with the mobile platform of the system. This is reflective of our theme of “development of digital competence”. It is possible that this is due to hypertensive patients being an older cohort of the population who are less likely to engage with newer information and communication technologies than younger people (Heart & Kalderon, 2013).

A recent meta-ethnography of digital interventions for self-management of chronic physical health conditions (Morton et al., 2017) concluded that patients who were engaging with these digital interventions felt reassured by the insight into their health that these tools provided. Specifically, in terms of hypertension, a recent thematic synthesis of patient and providers perspectives of on self-monitoring of BP (Fletcher et al., 2016) inferred that, for patients, self-monitoring was seen as balance between reassurance and anxiety. This is reflected in our

data, where some patients spoke of being motivated by the extra data and others were concerned about feelings of anxiety when readings were high. Fletcher et al. (2016) suggest that this uncertainty could be reduced by the patients and general practitioners (GPs) working together around how to interpret home BP values, how to adjust for home-clinic values, and particularly what values patients should get concerned at and when to act. This desire to work together with the GP was seen in the current data under the theme of sustainability.

Jolles, Clark, and Braam (2012) emphasize the importance of effective communication in a successful encounter between a hypertensive patients and their GP. Participants in this study felt that using the smartphone app could enhance their communication with their GP. This is reflected throughout the literature, with participants in the study by Hallberg, Ranerup and Kjellgren (2016) reporting that being able to visualize their BP values led to a better discussion at the consultation. This is in line with an empirical study by Ruckenstein (2014) which posits that making health data visible can add meaning to activities which can have an effect on this data. Making an asymptomatic condition like hypertension more tangible using imagery that the patient can make sense of is an approach that has been used to influence health relevant behavior in other health and illness contexts (Williams & Cameron, 2009).

Some studies involving GPs (Bradbury et al., 2017; Morrissey et al., 2017) have found a reluctance in practitioners to engage with these technologies due to fears around augmented workload and increased patient anxiety. Participants in the present study were very conscious of their GPs workload but saw this app as an opportunity to decrease it, as it meant that the GP could immediately be presented with up to date BP data. Bengtsson , Kasperowski , Ring and Kjellgren (2014) suggest that when using digital interventions GPs and patients need to understand each other's needs and circumstances and should concordantly agree on a treatment and treatment goal.

### **6.4.3 Strengths and weaknesses**

This study provides novel and timely data on hypertensive patients' perspectives of using smartphone apps to support self-management. Focus groups were an appropriate methodology to use for discussion around the usability of the app as they have high ecological validity and facilitate gathering of new knowledge around issues little is known about (Braun & Clarke, 2013) .

The multi-disciplinary research team coming together to review the data increased reflexivity but it is possible to also view this as another limitation as the team may have taken a different emphasis to that of an independent observer. These findings are consistent with others in the field (e.g. Morton et al., 2016) suggesting external validity. However, the sample was relatively small and from one geographical location so may not fully encapsulate the perspectives of all patients with hypertension. Additionally, while hypertension is typical of a chronic disease, it is possible that some of the challenges of other common chronic conditions such as diabetes or asthma were not captured in the data as the sample was limited to hypertensive patients.

### **6.4.4 Implications for research and practice**

This study recognized that while many of hypertensive patients are willing and eager to engage with smartphone apps to manage their hypertension, it is weighed against some concerns. Future research and development work should focus on how to make this type of intervention sustainable (e.g. Serrano, Coa, Yu, Wolff-Hughes, & Atienza, 2017), as many participants expressed doubts about maintaining app use over time. The limitations of technology to drive behavior change and the need to design long-term engagement strategies into these kinds of technology is well-recognized in this literature as sustainability is often identified as a key challenge (Alkhalidi et al., 2016; Donkin et al., 2011).

Patients engaging with these types of technologies may have the potential to increase the amounts of BP data available to GPs. This may lead to patients engaging in their healthcare in a more informed and patient centered way. Mudge et al. (2015) noted in a recent meta-synthesis that this shift in the power balance can be uncomfortable for some clinicians. Some strategies found to be helpful in this process of change included peer support, practicing reciprocity in communication style and self-reflection. The adoption of these types of technologies would also be easier if it was supported in a national eHealth infrastructure that is integrated into public health systems; however this is yet to be achieved in most international contexts including the present study context.

Participants did express some reluctance around healthcare apps in general, due to fears of misinformation or increases in anxiety. There is also evidence to suggest that commercially available apps for medication adherence have not benefitted from developments in the behavioral science of behavior change as they often have limited identifiable active ingredients in the form of recognizable behavior change techniques (Morrissey, Corbett, Walsh, & Molloy, 2016). The NHS Health Apps library in the UK provides patients with access to a list of endorsed apps, and this data highlights a need for a similar platform to be created by a health regulation body in Ireland and perhaps other contexts, given the potential uncertainty around the benefits and harms of these technologies.

#### **6.4.6 Conclusions**

Overall patients were divided in their views on using a smartphone app to self-manage their hypertension. Many could see the benefit of a medication reminder and felt that self-monitoring their BP would be empowering in terms of their understanding of the condition and in interactions with their GPs. However there were concerns around increasing health-related anxiety and doubts about the sustainability of this technology over time.

## **7. Discussion**

### **7.1 Discussion overview**

This chapter will present a summary of the overall findings of this research and evaluate the contribution made by this research to developing the evidence for digital interventions to enhance adherence to medication in people living with hypertension. The findings will be discussed in relation to existing literature regarding people with hypertension and interventions for this group. The implications of the findings for future research and practice will be described. The limitations of each study will be outlined and approaches to addressing these limitations will be suggested. Finally, this chapter will end with concluding remarks.

### **7.2 Summary of the overall findings of this research**

- The systematic review described in study 1 found tentative evidence to suggest that medication adherence interventions significantly lower blood pressure values. However, there was substantial heterogeneity amongst the included RCTs and many potential biases as the number of low risk of bias studies was limited.
- Despite efforts to identify which components of these interventions were associated with effect size, poor reporting standards meant that identifying these factors with the TDF was restricted which limited the analysis. The only domain that appeared to be significantly associated with reductions in SBP and DBP was ‘Memory, attention and decision processes’. However, this domain had been coded in most interventions, as the nature of being part of an adherence intervention study focuses the patients’ attention on their behaviour. Therefore, the only conclusion that can be drawn from this is that being part of a medication adherence intervention can lower blood pressure values, as seen in the meta-analysis.

- A subgroup analysis of the different types of interventions within the meta-analysis found that home blood pressure monitoring and technological interventions (mainly phone call or text message based) were associated with reductions in DBP, but not SBP. This lends tentative support to the hypothesis that a digital intervention incorporating home BP monitoring may be an effective way of managing adherence to anti-hypertensive medications.
- One of the greatest challenges of the systematic review was assessing risk of bias, extracting sufficient data to calculate effect size and coding interventions with the amount of information reported in papers.
- The content analysis of existing mobile phone applications in study 2 highlighted the lack of behavioural theory and evidence in commercially available medication adherence apps. However, it is worth noting that this study was conducted in 2015 and as the digital marketplace is rapidly changing and expanding, this may no longer be the case. Such analyses of the technology base are susceptible to almost immediate obsolescence due the speed of development of relevant hardware and software relevant to mobile self-management of medication.
- Both GPs (study 3) and patients with hypertension (study 4) could see benefit as well as expressing concern about a digital intervention such as a smartphone app with a medication reminder and home BP monitoring function. Both parties felt that BP data could empower them; GPs by making better clinical decisions and patients by gaining a deeper understanding of their condition. However, both also had reservations about the possible anxiety inducing nature of excessive self-monitoring.

### **7.3 Contribution of this research**

There is some evidence to suggest that medication adherence interventions are effective in reducing BP values in patients with hypertension (e.g. Conn et al., 2015). However, this had not been previously investigated to Cochrane standard. The findings of the systematic review in Study 1 suggest that, when only looking at RCTs conducted to a high standard and with minimal loss to follow-up, there is an overall positive effect of adherence interventions on BP values. Poor reporting of the RCTs included meant that the effective intervention components could not be identified. In this situation Glasziou, Chalmers, Green, and Michie (2014) recommend a number of approaches, one of which is to pick an intervention or create a composite version guided by a model of the mechanisms of the effect. There is a body of literature to suggest that the CS-SRM can be used to enhance medication adherence, particularly when taking habitual processes as well as treatment beliefs into account (Leventhal et al., 2008; Phillips et al., 2013).

While the use of the CS-SRM for enhancing medication adherence in hypertension is not novel, it remains unclear if it is feasible and acceptable to patients with hypertension to receive an intervention based on the CS-SRM principles on a digital platform. As outlined by Yardley et al. (2015) it is important that any DI is grounded in qualitative work with the users. By doing this with both service providers and the patients themselves, a valuable insight into both perspectives was gained, which will allow future research to take all stakeholder views into account.

### **7.4 Is retrospectively coding interventions with taxonomies and frameworks useful?**

In this research both the BCTTv1 and TDF were used to identify intervention components. The BCTTv1 was developed to provide a precise and systematic method of describing the active content of interventions with specificity (Michie et al., 2013). While the primary aim

of this taxonomy is to aid intervention design, it is also increasingly being used to retrospectively identify intervention components in systematic reviews (e.g. Fredrix, McSharry, Flannery, Dinneen, & Byrne, 2018; Gardner, Smith, Lorencatto, Hamer, & Biddle, 2016). However, the work of study 2 which involved coding medication adherence apps with BCTTv1 highlighted some limitations with using the taxonomy in this way. Firstly, coding the BCTTv1 requires the coder to code a “0” if the BCT is absent, “1” if it is probably present and “2” if it is definitely present. This method does not account for dosage i.e. how frequently or intensely the BCT is presented. In the case of study 2, most apps were coded with the BCT “Prompts/cues” but no distinction could be made between apps that contained frequent reminders that persistently appeared on the users’ home screen or apps that sent a single dismissible reminder notification. It is likely that these two types of reminders could impact differently on behaviour. The dichotomous present/absent nature of coding with the BCTTv1 cannot account for this. On this point Peters, De Bruin, and Crutzen (2015) argue that the BCTTv1 only captures a segment of what theory states about active content of interventions. Another limitation, this time specific to using the BCTTv1 to code interventions that are outlined in a published paper (in this case smartphone apps) is that some of its concepts don’t fully translate to the digital intervention domain. For example, it would be difficult to digitally substitute the BCT “Adding objects to the environment” as it requires physical objects to be added to the environment to facilitate the behaviour.

The TDF is different to the BCTTv1 as it is an integrative framework which was developed and validated to summarise the range of psychological theory underpinning behaviour change into distinct factors (Cane et al., 2012). However, it is possible to use it in a similar manner, by coding interventions with its distinct domains. This was done in study 1 and again, challenges with coding arose. One particular difficulty with using the TDF was the relationship between domains. Not all constructs fall into distinct domains, for example,

‘action planning’ is a construct in both ‘goals’ and ‘behavioural regulation’. This problem has been identified by Little et al. (2015) when trying to clarify the boundaries between some domains when using the TDF as a coding framework. Therefore, while the TDF is a useful tool for examining the content of interventions the discriminant validity of some of the domains may need refinement.

The other main difficulty was that the coding had to be based on inference from the text, as very few studies reported the explicit use of theory. Many studies did not report the intervention and control group content in detail, with most just describing the control as “usual care”. This meant that the coding may not have been an accurate representation of the content of the intervention or the control. This challenge has also been observed when coding interventions with the BCTTv1 (Knittle et al., 2018; Pesseau et al., 2015). Additionally, even if the intervention is well reported, this retrospective coding does not capture fidelity – the extent to which the intervention component was delivered accurately and uniformly to all participants (de Bruin, Crutzen, & Peters, 2015). A final limitation with this approach is that even with high fidelity of delivery, performance of the BCTs by participants may be suboptimal, which could also affect outcomes (Hankonen et al., 2014). As a result of these observed limitations, there has been a call amongst the health psychology community to improve reporting of intervention development and evaluation (Knittle, 2015). It does seem that when reporting improves and taxonomies and frameworks like the BCTTv1 and the TDF are used to describe the active ingredient of interventions, it will become easier to synthesise behaviour change evidence (Pesseau et al., 2015).

### **7.5 Application of the extended CS-SRM and experiential feedback to this context**

As discussed in the introduction, Phillips et al. (2016) have proposed extending the CS-SRM to include behavioural habit strength as a factor important for maintenance of behaviour. In a

previous study (Phillips et al., 2013) they posit that an important factor in creating habit strength is ‘CSM coherence’. This is defined as a certainty in one’s beliefs regarding the illness and treatment that is a result of direct, personal experience that a treatment works to control the illness. (It is worth highlighting that this definition is at odds with the illness coherence sub-scale of the popular psychometric tool-the illness perception questionnaire-revised (Moss-Morris et al., 2002) which emphasises the beliefs of patients and not their experiences or the effect of their treatment experiences on their beliefs.) If the performance of the treatment results in evidence that it is working and therefore confirms the patient’s beliefs, their CS-SRM model becomes coherent. This can be difficult to achieve in asymptomatic conditions such as hypertension, due to the lack of physical feedback to the treatment. However, work in Type 2 diabetes has shown that patients use their blood glucose meters as a source of feedback on how their self-management efforts are working (Tanenbaum et al., 2015). A meta-ethnography by McSharry, McGowan, Farmer, and French (2016) found that some patients with Type 2 diabetes were actively engaging with their blood glucose monitor as a representation of their treatment by only using medication when their blood glucose was reported to be high.

Like blood glucose monitoring, home BP monitoring could possibly be used in hypertension as a proxy for physical feedback. This came up in study 4, under the ‘Rules of Engagement’ theme with one focus group participant saying about his BP monitor, “*The presentation gives you a constant read and you can always check back... Just to see how things are*”. One of the GPs in study 3 also commented on BP monitoring, “*...the action of recording and inputting means the patients probably buy in a bit more. So you would expect their compliance to be a lot better if that was the case*”. Phillips et al. (2013) investigated this further by examining whether patients with hypertension’s reports of receiving experiential feedback that their medication works predicted medication adherence and found that it only predicted intentional

non-adherence. They suggested that it was possible that CS-SRM coherence is not important for predicting behaviour in the long term, or it may only be important for predicting intentional non-adherence among those who are persistent. One of the subgroup analyses in the systematic review and meta-analysis (study 1) also lends tentative support to this as it was found that home BP monitoring was significantly associated with reductions in DBP.

In study 2 the content analysis of smartphone apps revealed that only a minority of applications used behaviour change techniques (BCTs) beyond "action planning" and "prompt/cues". These BCTs can facilitate the formation of habits, however these are only likely to be useful when patients want to take their medication and have a cognitive representation of their illness and treatment that is largely consistent with that. Many apps may therefore assume motivation in the reflective sense of the word, as opposed to the impulsive meaning that would incorporate strong cue-response associations (Michie, van Stralen, & West, 2011). As a result, there is currently relatively limited application of the extended CS-SRM and experiential feedback to DI development to support medication adherence. While some apps did include "self-monitoring" and "feedback" the design of these interventions was not consistent with the development of 'coherence' through experiential feedback as identified by Phillips and colleagues in the extended CS-SRM (Phillips et al., 2016; Phillips et al., 2013). Therefore, app development has not benefited from the rich theoretical developments in health psychology which outline key self-regulatory processes in the self-management of illness.

Taken together, these findings in the thesis and the wider literature show that the extended CS-SRM and the role of experiential feedback within it have some unexplored potential.

There is scope to further our understanding of adherence behaviour, particularly in relation to the design and evaluation of DIs where there is currently a relative absence of evidence that has been theoretically informed by approaches from health psychology.

The recent proliferation of DIs and connected and portable BP monitors provide an ideal opportunity for this work. In particular, there are new means of measuring behaviour in real time and intervening to support adherence that are facilitated by these technologies e.g. just in time interventions (Nahum-Shani et al., 2016). These developments will enable more sophisticated applications and evaluations of the extended CS-SRM and experiential feedback into research designs.

## 7.6 Implications for research

This research has developed the evidence base for a DI for medication adherence in hypertension. The next stage of the MRC guidelines in the development and evaluation of complex interventions is feasibility/piloting (Craig et al., 2008).

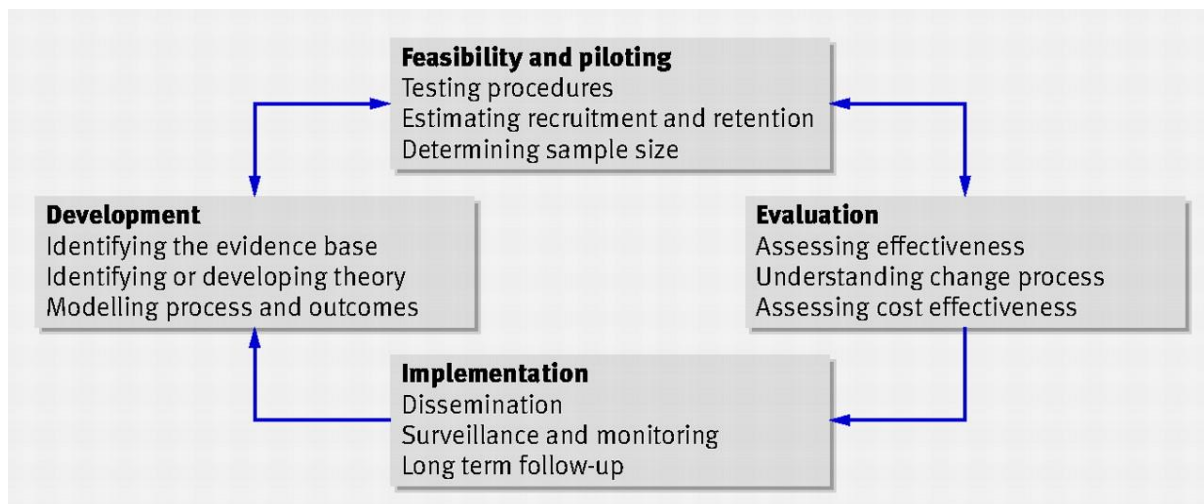


Figure 7.1. The MRC guidelines for the development of complex interventions

The person-based approach (Yardley et al., 2015) recommends that once a DI has been planned and a prototype version created, more qualitative work must occur to assess this feasibility. This can explore if the DI is acceptable, interesting, persuasive, easy to use and feasible for people to adhere to. This could be easily applied in the current research; patients with hypertension could be asked to use the MiBP app, described in Study 4, for a specified period of time, and then interviews about their experience could be conducted. As Yardley et

al. (2015) recommend, this user feedback could then be used to change the DI as appropriate and then further interviews conducted to check the suitability of these changes. This process needs to be iterative as the current social context means that DIs can quickly look dated and users will expect different ways of interacting with them depending on what functionalities and aesthetics are common at the time (West & Michie, 2016). Indeed, the idea of sustainability as time progresses was seen as a theme in study 4, with patients making suggestions about how the DI could be changed or updated over time.

One change that could possibly be implemented in this DI is the use of action plans alongside with or rather than reminders. As reminders are common in medication adherence apps, they were chosen as a means of addressing habitual behaviour. However as habitual action is performed when conditioned contextual cues are encountered, it may be of more benefit to use a planning intervention that is based on context, such as action planning or implementation intentions. These refer to a process of consciously considering and deciding upon actions to take in pursuits of a goal and typically involve mentally pairing expected environmental cues with intended actions (Hagger & Luszczynska, 2014). O'Carroll et al. (2014) found implementation intentions to be effective in improving medication adherence amongst stroke survivors. There is considerable scope for action planning and implementation intentions in DIs. This is particularly evident in the asthma self-management literature, where there are several studies and reviews of action planning apps (e.g. Morrison, Mair, Yardley, Kirby, & Thomas, 2017; Odom & Christenbery, 2016; Perry et al., 2017)

Once the DI is considered acceptable to the user the next stage of this research would be a feasibility trial or a pilot RCT, according to the MRC framework. A feasibility trial would allow the processes of carrying out a larger trial to be tested and make final refinements before effectiveness is tested in a fully powered RCT (Bradbury, Watts, Arden-Close, Yardley, & Lewith, 2014). Another appropriate method in this case may be the multiphase

optimisation strategy (MOST; Collins, Kugler, & Gwadz, 2016). MOST is a three phase – preparation, optimisation and evaluation – framework which emphasis optimisation before the evaluation with a fully powered RCT. The preparation phase includes assessment of the literature, development of a conceptual model, identification of intervention components, and completion of pilot studies to examine the feasibility and acceptability of intervention components. Optimisation is a process that uses fully powered, efficient, randomized experimentation to gather information about the individual and combined performance of intervention components to identify one of the best possible combinations that is effective at addressing the public health problem at hand (Kugler, Balantekin, Birch, & Savage, 2016). Optimisation would be an appropriate next step for the current research to take. The individual effects of the intervention components of BP monitoring, reminders and/or action planning and the interactions between them could be examined through a fractioned factorial design. This involves each component having two levels: on (included in the intervention package) and off (not included). This presentation or removal of intervention components could be easily achieved in DI. A fractional factorial design also means that far less participants are required than a traditional experimental design (Collins et al., 2016). MOST has been used in a number of different contexts such as infant feeding (Kugler et al., 2016), smoking cessation (Baker et al., 2016) and obesity (Pellegrini, Hoffman, Collins, & Spring, 2014) and is seen as an efficient way to assess the feasibility of components prior to testing them with a fully powered experiment.

A final consideration for future research is the development of digital hardware. Medication adherence measuring technology is rapidly progressing, with the introduction of digestible sensors placed inside medication (Hafezi et al., 2015) and smart necklaces to detect the swallowing of medication (Kalantarian, Alshurafa, Le, & Sarrafzadeh, 2015). Already attempts have been made at integrating BP monitoring into a smartphone device. Plante,

Urrea, MacFarlane, and et al. (2016) investigated the accuracy and precision of the popular app Instant Blood Pressure. This app estimates blood pressure (BP) using a technique in which the top edge of the smartphone is placed on the left side of the chest while the individual places his or her right index finger over the smartphone's camera. They found its BP measurements to be highly inaccurate, with 77.5% of participants with hypertension receiving a BP value in the non-hypertensive range. However, there is no doubt that both this technology and medication adherence technology will keep evolving and it is crucial that research is conducted on both its accuracy and its acceptability and feasibility to patients' over time.

### **7.8 Implications for practice**

The majority of hypertension care happens in the community at general practice consultations in Ireland and many other contexts internationally. The results of study 3 showed a reluctance among GPs to engage with newer technologies such as a smartphone based DI. This reticence is likely to change if the emergence of newer technologies was accompanied by the emergence of an evidence base demonstrating effectiveness and cost-effectiveness, along with clear regulation and data protection systems. In particular, GPs would need to be convinced that engaging with these technologies does not add to their current workload and ideally contributes to reducing it. eHealth Ireland is a relatively recent addition to the national Health Service Executive's strategy and its work to date has focused on the development of the national electronic health record. Future work should have a role in quality control and the provision of explicit guidelines in relation to such digital interventions. Examples of this that already exist are the NHS Health Apps library (<https://apps.beta.nhs.uk/>) in the UK which provides patients with access to a list of recognised and endorsed health apps.

Michie, Atkins and West (2014) suggest that the design and delivery of any intervention should be evaluated using the APEASE criteria (affordability, practicability, effectiveness and cost-effectiveness, acceptability, side-effects/safety, and equity). In practice, DIs for hypertension such as the one examined in study 4 meet several of the criteria. Firstly, following initial set-up costs, it is likely to be affordable given the scalability of delivery and the reduced face-to-face costs. It also allows for the intervention to be delivered as designed and is likely to be cost-effective when compared to face-to-face interventions. Work has been done on acceptability (study 3 and 4) and future research can develop these findings to make the DI more acceptable to all stakeholders. Side effects and safety must also be taken into consideration in future work. The final criterion of equity may be the most relevant to this DI as all intended recipients must have broadly equal access to the digital technology required. As people with hypertension tend to be an older population who have lived much of their lives without a mobile device this may be a concern. However ownership of mobile devices is constantly increasing, with 54% of people over 65 in Ireland owning a smartphone in 2017, compared to 48% in 2016 (Deloitte, 2017). As long as this trend continues and smartphone use does not become socioeconomically patterned with respect to age, education, income or wealth, concerns around the equity of DIs as a mode of intervention delivery will decrease.

## **7.9 Strengths and limitations**

This study has a number of strengths and limitations which are outlined below.

The systematic review and meta-analysis on interventions for medication adherence in hypertension described in study 1 was a hypertension specific update to the Cochrane Review by Nieuwlaat et al. (2014) on interventions to enhance medication adherence. It was based on a pre-registered and published protocol (Morrissey et al., 2016) and was conducted to the Cochrane standard. All screening, data extraction, assessment of risk of bias and coding with

the TDF was done independently by two authors, with a third author adjudicating across all work. The literature search was comprehensive (see Appendix II) and included several databases and trial registries. Due to the review being an update, we carried forward the eligibility criteria of the previous review, which aimed to summarise the current best evidence of unconfounded RCTs, with at least 80% follow-up in all treatment groups, assessing the effect on both adherence and clinical outcomes. The exclusion of studies with less than 80% follow up could be seen as a limitation as it may have resulted in otherwise high quality studies being excluded from the review. It is possible that the results may have been different if a larger loss to follow up had been allowed. However, Schulz and Grimes (2002) suggest that over 20% loss to follow up can threaten trial validity and a systematic review of all trials funded by the NIH Health Technology Assessment Programme examined 151 RCTs and found that the median retention rate was estimated to be at 89% (Walters et al., 2017), providing justification for the required 80% follow up.

The findings of a systematic review are only as reliable as the studies included in the review (Garg, Hackam, & Tonelli, 2008) and there were some methodological issues in the studies included in this review. While each of these studies met the inclusion criteria and contributed to answering the research question, they were quite heterogeneous in content and quality as can be seen in the risk of bias assessments. Additionally, many of them were poorly reported, meaning that the interventions may be misrepresented in this review. These issues should be considered in interpreting the findings and applying them to future studies.

The second study involved a content analysis of medication adherence apps using the BCTTv1, limitations of which are discussed above. While this study was the first to do so, and provides valuable information about the implementation of behavioural science in apps, it did not provide a comprehensive overview of the quality of the apps. As the BCTTv1 does not express how the BCTs are implemented (e.g. “2.2 feedback on behaviour” could be

present as a simple calendar log or a detailed graph of adherence), and also does not capture how engaging, functional or aesthetically pleasing the delivery of the BCT is within the app, it may have been of benefit to include an additional tool in the content analysis. The Mobile App Rating Scale (MARS; Stoyanov et al., 2015) is a scale designed for assessing the quality of health apps. It is a 23 item scale with four objective quality scales: information quality, functionality, engagement and aesthetics; and one subjective quality scale. The inclusion of a multidimensional measure such as this, alongside the BCTTv1 may have provided a more detailed and useful overview of current medication adherence apps.

In both the third and fourth studies, attempts were made to avoid bias in how the data was collected and analysed. Topic schedules were created beforehand (see Appendices IX, XII and XIV) and were followed during both studies. General questions were asked before specific ones and the questions were designed to be neutral and answerable. Efforts were made to ensure the participants were as comfortable as possible by conducting the interviews and focus groups in familiar settings (GPs own clinics and Croí House) and providing refreshments and brief informal introductions. The equal representation of participants from urban and rural backgrounds was a particular advantage as it allowed these different contexts to be examined. However it is possible that factors such as the moderators age, social status, race and gender may have led to bias (Braun & Clarke, 2013).

The author of this thesis was both the interviewer in study 3 and moderator in the focus groups in study 4 and also led the analysis of both. Factors such as the researchers' beliefs, goals, experiences and personality could have led to a subjective interpretation of the results. However, as the nature of qualitative work requires personal reflexivity, this was acknowledged throughout the data collection and analysis. The coding of the data was partially done by another researcher and the study team came together to generate the initial themes, heightening reflexivity. As these studies were grounded in the sematic realist

approach and intended to be exploratory and descriptive in nature, just one interview or focus group was conducted with each participant. However, additional insight may have been gained through follow up interviews. This would also have allowed for the validity of emerging themes to be checked.

In high-quality digital intervention development, an app is usually designed based on theory and the findings of systematic reviews and initial qualitative work (Yardley et al., 2015). However, due to time and resource constraints for app development this was not possible in this case. Significant efforts were made to select an app that fitted in with the theory and findings of study 1 and 2 from this work. The app that was used, MiBP, was considered a good choice as it was developed from qualitative work with people with hypertension (Glynn et al., 2015). Additionally, it contains both a home BP monitoring function and a reminder device, which may influence both the reflective system through experiential feedback and automatic system through habit formation, as outlined in the CS-SRM.

## **7.10 Conclusion**

DIs for self-management of hypertension already exist, although few are grounded in evidence or have availed of theory and approaches from the behavioural sciences. The use of theory, systematic review and qualitative work in this thesis means that this research was an appropriate enhancement of the evidence base for a DI for medication adherence in hypertension. Therefore the new evidence that has emerged from these 4 studies provides a platform for future intervention development to support adherence to anti-hypertensive medication.

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## **Appendices**

### **Appendix I: Protocol of systematic review as published in *BMC Systematic Reviews***

#### **Effectiveness and content analysis of interventions to enhance medication adherence and blood pressure control in hypertension: A systematic review and meta-analysis.**

Morrissey, E.C.<sup>1</sup>, Durand, H.<sup>1</sup>, Nieuwlaat R.<sup>2</sup>, Navarro, T.<sup>2</sup>, Haynes, R.B.<sup>2</sup>, Walsh, J.C.<sup>1</sup> & Molloy, G.J.<sup>1</sup>

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## **ABSTRACT**

### **Background**

Hypertension control through pharmacological treatment has led to substantial benefits in the prevention of morbidity and mortality from cardiovascular diseases. However, evidence from a number of studies suggests that as many as 50% to 80% of patients treated for hypertension are have low adherence to their treatment regimen. The objective of this systematic review is to evaluate the effectiveness of medication adherence interventions for hypertension. In addition we aim to explore what barriers and facilitators in the interventions may have been targeted and how these might be related to the effect size on blood pressure (BP).

### **Methods**

This review is a hypertension-specific update to the previous Cochrane Review by Nieuwlaat et al. (2014) on interventions to enhance medication adherence. A systematic literature search will be carried out and two authors will independently screen titles and abstracts for their eligibility for inclusion and independently extract data from the selected studies and

assess the methodological quality using the Cochrane Collaboration Risk of Bias Tool. A meta-analysis will be conducted and additionally, theoretical factors in interventions will be identified using the Theoretical Domains Framework.

## **Discussion**

This review will generate new information by quantitatively evaluating the effectiveness of adherence interventions for hypertension and potentially identify which theoretical domains are associated with more effective interventions and which domains have not been the subject of intervention development.

## **Trial registration**

This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42016033358) on 26<sup>th</sup> January 2016.

## **KEYWORDS**

Hypertension, medication adherence, blood pressure, compliance

## **BACKGROUND**

### **Rationale**

#### *Description of the condition*

Hypertension, also known as high or raised blood pressure (BP), is a condition in which the blood vessels have persistently raised pressure. Epidemiologic studies demonstrate that cardiovascular disease events (e.g. stroke, heart failure and coronary heart disease) are associated with hypertension (Amici et al., 2009; Pini et al., 2008) A systematic review by Kearney et al. (2005) found it to be an important risk factor for more serious conditions that carry greater risk of disability and death (primarily cardiovascular and cerebrovascular

events) and the single most important modifiable risk factor for stroke and myocardial infarction in both developed and developing countries. It is estimated that hypertension affects one billion people worldwide (Alwan, 2011).

Hypertension control through pharmacological treatment has led to substantial benefits in the prevention of morbidity and mortality from cardiovascular disease (Wright & Musini, 2009). A Cochrane review by Musini et al. (2009) conducted an assessment of all the trials of blood pressure lowering therapy in people with hypertension aged 60 years and over and found that these treatments reduced death, strokes and heart attack. However, despite the efficacy of anti-hypertensive agents, there is a significant problem of non-adherence to these medications in those diagnosed with hypertension, therefore the effectiveness of current treatment is limited.

The World Health Organisation (WHO) defines adherence to long-term therapy as “the extent to which a persons behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider” (Sabaté, 2003). High adherence (defined as medication possession ratio of 80 % to 100%) to hypertensive medications is associated with higher odds of blood pressure control compared with those with medium or low levels of adherence (Bramley et al., 2006). Evidence from a number of studies suggests that as many as 50% to 80% of patients prescribed pharmacological antihypertensive therapy have low adherence to their treatment regimen (Elliott, 2008). Vrijens et al. (2008) used medication event monitor system (MEMS) data to measure adherence to antihypertensive medications and found that about half of all patients prescribed the medications stopped taking them within one year of the initial prescription. They also found that on any one day, 10% of patients omitted their scheduled dose of medication. According to the WHO, this lack of adherence to antihypertensive medication is the most important cause of failure to achieve BP control (Sabaté, 2003).

### *Description of the interventions*

Interventions for enhancing medication adherence in hypertension can have multiple components, such as education around the condition and the importance of adherence, skills development, combination pills, provision of practical support and self-monitoring of blood pressure. These interventions have had mixed results (e.g. Amado Guirado et al., 2011; Matsumura et al., 2012). Vicki S Conn et al. (2015) conducted a meta-analysis combining randomized and non-randomized studies that targeted anti-HT medication adherence improvement and found that 112 intervention vs control group comparisons had a standardised mean difference effect size of 0.3 (SD 0.079) on adherence. However there was significant heterogeneity across studies ( $I^2 = 87\%$ ), which can be explained by heterogeneity in samples, designs and measures used to assess adherence.

### *How the intervention might work*

Because interventions for adherence in hypertension can have very varied and often multiple components, it can be difficult to ascertain which factors are causing the intervention to work or are masking effective components. Behavioural theory can be used to gain an understanding of the effects of the behaviour change intervention. However, papers rarely report the explicit use of theory despite interventions almost certainly involving at least an implicit idea of what factors to address to instigate change (Little et al., 2015). This means that even if an intervention is successful, it is difficult to understand the behaviour change processes responsible and therefore to inform future intervention design, refinement and application. Consequently, it may be of benefit to retrospectively identify which barriers and facilitators adherence interventions report targeting, and the extent to which such factors map onto pre-existing theoretical factors. In order to capture the potential range of possible targeted factors, a sufficiently broad framework of theoretical factors is required. The Theoretical Domains Framework (TDF) is an integrative framework which was developed

and validated to summarise the range of psychological theory underpinning behaviour change into distinct factors (Cane et al., 2012; Michie et al., 2005); By applying the TDF to adherence interventions, it may be possible to explore which theoretical domains modify effect size (e.g. Cahir et al., 2015; Little et al., 2015).

### *Why it is important to do this review*

There are two reasons why it is important to do this review. Firstly, it is a hypertension-specific update to the previous Cochrane review by Nieuwlaat et al. (2014) on interventions to enhance medication adherence. This was an extremely large review, encompassing all medical conditions. Due to the heterogeneity of outcomes across conditions, it was not feasible to conduct a meta-analysis as part of the research. As this study is focusing specifically on hypertension, it is anticipated that most of the included interventions will have a common outcome of change in blood pressure in addition to the outcome of medication adherence. This will allow quantitative synthesis and additional analysis that was not possible in the previous review. Secondly, to the best of our knowledge, identifying whether the targeting of particular theoretical domains in the interventions is associated with greater effect sizes in adherence interventions in hypertension has not been done previously. Recent studies have attempted to synthesise existing evidence using a similar general approach (e.g. Little et al. (2015) used the TDF within a systematic review of interventions to improve quality of care in post-fracture investigation.) This will be a valuable addition to the literature as it may inform future intervention design.

### **Objectives**

The objective of this review is to evaluate the effectiveness of adherence interventions for hypertension and explore which specific barriers and facilitators the interventions may have

been targeting and how this tailored approach might be related to the effect size on blood pressure (primary outcome) and medication adherence.

## **METHODS**

### **Eligibility criteria**

This protocol has been developed in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement (David Moher et al., 2015) (see Table 1). The systematic review and meta-analysis will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (David Moher, Liberati, Tetzlaff, Altman, & The, 2009) and is registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42016033358).

Table 1.

*PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page no in manuscript
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3 & 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9 & 17
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12 & 13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	12 & 13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

### *Types of studies*

The systematic review is a condition-specific update to the large review by (Nieuwlaat et al., 2014) on interventions to enhance medication adherence which searched for studies until January 2013. This review will include randomised controlled trials (RCTs) that provide unconfounded tests of interventions expected to enhance adherence. Studies will be included regardless of treatment intensity or duration, mode of treatment delivery or medium of treatment.

### *Types of participants*

Patients who were prescribed medication for hypertension.

### *Types of interventions*

Interventions of any sort intended to affect adherence with prescribed, self-administered medication for the treatment of hypertension.

### *Types of outcome measures*

The primary outcome will be the change in blood pressure (SBP, DBP, or both) at six months compared with baseline readings taken prior to the intervention. The change in BP may be reported as a dichotomous (% with positive/negative BP change) or continuous variable (mean change in BP values). The primary outcome will be compared between treatment groups, i.e. the difference between groups regarding the change in BP.

The secondary outcome will be medication adherence measured by at least one of the following: self-report, pill count, pharmacy refill records, electronic medication monitors (MEMS).

Interventions will have to include both outcomes to be included.

### *Follow up completion*

Regarding follow up completion, studies will need to have at least 80% follow-up during at least six months. The 80% data completion is required for both blood pressure and adherence outcomes.

## **Information sources**

### *Search methods for identification of studies*

We will search *The Cochrane Library* including CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL and Sociological Abstracts. This database search will be a hypertension specific update on previous searches that were undertaken on: 1 September 1993; 12 December 1993; 1 June 1994; 30 June 1995; 31 July 1998; 15 August 2001; 30 September 2004; 1 February 2007 and 11 January 2013. We will search new publications since 11 December 2012, that is, having a one-month overlap with the previous search. All databases were originally searched from their start date. Ongoing trials will be identified by checking trials and protocols published in relevant databases of current ongoing clinical research studies, specifically World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov.

## **Search strategy**

The search filters for each database can be seen in Appendix 1. We will check articles cited in reviews and original studies of patient adherence in hypertension. We will contact authors of included RCTs to identify additional studies.

## **STUDY RECORDS**

### *Data management*

We will use a web-based data management system, developed by the Health Information Research Unit at McMaster University to facilitate screening, data extraction, adjudication of disagreements, author review and confirmation of data, production of data tables, and production of data files for future research use. This system has been successfully used in conducting and completing several large, complex systematic reviews.

#### *Selection process*

We will re-assess all RCTs on hypertension included in the 2014 update for eligibility to carry over into the current update. Retrieved citations from the updated search will enter a first screening stage. Based on the title and abstract, studies will move to the second screening stage if they meet all five eligibility criteria or if there is uncertainty about their eligibility. In the second screening stage, assessment of the full text will determine if studies will be included on the review. At both screening stages, two independent review authors (EM and HD) will assess eligibility and an adjudicator (TN) will resolve disagreements. We will record reasons for excluding citations in the second screening stage and report these in a PRISMA flow chart.

## **DATA COLLECTION AND ANALYSIS**

#### *Data collection process*

We will import data from the 2014 review into the update database and check the data for accuracy. Extracted data includes items as provided in the tables from the previous review (Nieuwlaat et al., 2014): the ‘Characteristics of included studies’ table (i.e. methods, participants, interventions, outcome, additional notes pertaining to any one of the aforementioned items, detailed assessment of risk of bias), the ‘Adherence and outcome’ table (i.e. intervention, control, effect on adherence outcome, effect on clinical outcome) and

risk of bias summary. We will extract the same items for the new included studies. Two review authors (EM and HD) will independently extract all new data and an adjudicator (TN) will resolve disagreements. We will contact primary or corresponding authors of all included RCTs to confirm extracted data and provide missing data.

The TDF domains that appeared to be targeted by the interventions and within the control groups will be identified and coded independently by two reviewers (EM and GM), using a data extraction form designed for the purpose (Appendix 2). We will use domains as well as constructs within domains to inform coding decisions within domains, using construct definitions as described by Cane et al (2012). The data extraction form will be tested on one included study. The coding of each domain will be supported by evidence from the text. Inter-rater reliability will be calculated prior to resolving discrepancies. Discrepancies will be discussed until 100% agreement is achieved.

#### *Assessment of risk of bias in included studies*

Two authors (EM and HD) will independently use the Cochrane 'Risk of bias' tool described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011) to assess randomisation procedures, bias, allocation, outcome assessors, reporting of findings and losses to follow up.

#### *Measures of treatment effect*

For the primary outcome of BP, we will report mean differences between groups and the 95% confidence intervals (95% CI).

For the secondary outcome of medication adherence, it is likely that different measurement tools will have been used and so we will calculate the standardised mean difference and the 95% CI for continuous data.

Where no standard deviations are reported, we will calculate the standard deviations using the methods described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins, 2011).

#### *Unit of analysis issues*

In studies where more than one intervention group is contained in one comparator arm we will include both interventions (providing they are relevant to the review) and will split the number of participants between the two groups accordingly. Where cluster RCTs are included for analysis we will use appropriate statistical analysis methods to account for the cluster effect as described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011).

#### *Assessment of heterogeneity*

We will use the  $I^2$  statistic and the  $\text{Chi}^2$  test to assess heterogeneity as described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011). We will initially carry out a qualitative analysis of the heterogeneity of the study groups by study design e.g. number of randomised groups and data collection methodology e.g. measurement strategy to assess adherence. We will quantitatively analyse suitable data subsequently using regression analysis.

#### *Assessment of reporting bias*

We will assess reporting bias initially by a visual inspection of funnel plots and use of appropriate statistical tests as described in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011). Some studies may not report absolute blood pressure changes, but rather proportional changes from the baseline measurement or another parameter. In these cases we will also consider reporting bias.

### *Data synthesis*

Data will be pooled and analysed where appropriate and feasible. We will analyse each outcome measure separately, calculate intervention effects and express them as relative risks with 95% confidence intervals for dichotomous data, and as mean differences and standardised mean differences (if required) with 95% confidence intervals for continuous data. We will give consideration to the use of random-effects models that can be incorporated into the statistical analysis if substantive statistical heterogeneity is identified. In addition, we will use subgroup analyses to assess heterogeneity (see below).

The relationship between the number of *different* domains coded and the effect size of the intervention will be explored using Pearson correlations (two-tailed). This analysis will be based on similar work by Little et al. (2015). The maximum possible number of different domains coded will be 14 (the number of TDF domains). The number of different domains coded in the control group will be subtracted from the number of different domains coded in the intervention group. A sensitivity analysis will be performed in which the subtraction of control groups was not done, to examine the effect of the subtraction on the result. The analysis will also explore the potential for weighting domains according to the frequency of which the domain was targeted. If no significant difference emerges, the primary approach to data synthesis will be descriptive e.g. identifying the proportion of studies that target specific domains.

### *Subgroup analysis*

We anticipate that different categories of interventions will be used by the included studies, including context of the intervention delivery, technological interventions, combination pill and service provision interventions. If appropriate, we will use subgroup analysis to categorise these interventions and to explore heterogeneity. Similarly, some studies may only

target low adherers while others target all hypertension patients. If numbers allow, subgroup analysis will also be conducted here. If feasible, similar patient sub-group analysis will also be conducted on age and gender.

## **DISCUSSION**

This proposed review will add to the literature in several ways. Due to population growth, ageing and behavioural risk factors, such as unhealthy diet, harmful use of alcohol, lack of physical activity, excess weight and exposure to persistent stress, there has been a significant growth in the incidence of hypertension; the number of people with hypertension rose from 600 million in 1980 to 1 billion in 2008 (Organization, 2014). Issues around the control and management of hypertension are becoming increasingly pertinent, in high income countries and even more so in low and middle income countries.

As previously discussed, interventions for medication adherence in hypertension tend to be multi-factorial and there is no ‘one’ recommended strategy for enhancing adherence (Nieuwlaat et al., 2014). It is possible that by mapping intervention components to the TDF we may be able to determine which theoretical factors are associated with larger effect sizes. A systematic review, also using the TDF, by Khatib et al. (2014) examined patient and healthcare provider barriers to hypertension awareness, treatment and follow-up. While this analysis of quantitative and qualitative studies provides valuable information, it is possible that self-reported barriers are not always the critical determinants of non-adherence, and therefore interventions targeting these factors may not be effective. This current review will be an important follow up on to this, as we will be able to see if the barriers and facilitators reported by the patients and providers are the same barriers and facilitators that have been targeted in intervention RCTs and which intervention targets are associated with larger effect

sizes. This will have a stronger potential to inform future intervention development and clinical practice in the area.

There are limitations to retrospectively coding interventions. It is likely that some of the interventions will not employ or fail to report explicit use of theory, as seen in a similar systematic review on adherence by Holmes, Hughes, and Morrison (2014). This means that coding will have to be based on inference from the text. This may also be challenging as preliminary review of some of the relevant interventions show that some of them are lacking comprehensive descriptions of the intervention content. However, all authors will be contacted and asked to provide more information and intervention manuals where possible. Also, coding will be carried out by two reviewers to allow for better sensitivity and enhanced reliability of the theoretical content. Another limitation of this review is that it only includes RCTs. This is the highest quality evidence, but large population and policy interventions are typically not tested in RCTs and thus not captured. As organizational/policy interventions are part of a wider approach to behaviour change intervention, our focus on RCTs where individuals or clusters are randomised to treatments is appropriate. Using a more homogenous set of study designs and intervention approaches would lead to a less coherent and defensible synthesis of study findings. This review will provide the highest quality evidence for specific intervention techniques that should be part of larger programs of policies, if proven effective. A final limitation is the observational nature of this work, any association found between domains and effect size will be correlational and as such, causation cannot be inferred.

This review will be of interest to researchers, health professionals, healthcare commissioners and patient groups. It will generate new information by quantitatively evaluating the effectiveness of adherence interventions for hypertension and potentially

identify which theoretical domains are associated with more effective interventions and which domains have not been the subject of intervention development.

## **DECLARATIONS**

### **Abbreviations**

BP: blood pressure EM: Eimear Morrissey DBP: diastolic blood pressure GM: Gerard Molloy HD: Hannah Durand MEMS: medication event monitoring system PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses PROSPERO: International prospective register of systematic reviews RCT: randomised controlled trial SBP: systolic blood pressure TDF: theoretical domains framework TN: Tamara Navarro WHO: World Health Organisation

### **Ethical approval and consent to participate**

Not applicable.

### **Consent for publication**

Not applicable.

### **Availability of supporting data**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

EM carried out the initial background research and conceived of the study. EM also drafted the manuscript. GM, RN and RBH helped in drafting the manuscript or revising it critically for important intellectual content. HD, TN and JW made substantial contributions to the conception and design of the project, including revising the manuscript. All authors gave final approval of the version to be published.

### **Acknowledgements**

Not applicable.

### **Authors' information**

EM, HD, JW and GM are part of the Medication Adherence Across the Lifespan (MEDAL) group at the School of Psychology at the National University of Ireland, Galway.

RN, TN and RBH are part of the Department of Clinical Epidemiology and Biostatistics at McMaster University, Canada. All three are involved in the Cochrane Review on interventions to enhance medication adherence.

## Appendix II: Systematic review search strategy

**MEDLINE** search filters used in this update using the Ovid interface:

1. ((exp patient compliance/ OR (patient adj compliance).tw. OR (patient adj adherence).tw. OR (medication adj compliance).tw. OR (medication adj adherence).tw.) AND ((clinical trial OR random:).mp. OR tu.xs.)) NOT ((qualitative OR retrospective OR mice OR rat OR rats).tw. OR editorial.pt. OR letter.pt. OR comment.pt.) NOT (animals NOT humans).sh.  
(Note: clinical trial.mp. picks up clinical trial.pt.)
2. ((random: OR control:).mp. AND (exp patient compliance/ OR patient dropouts/ OR psychotherapy/ OR treatment refusal/ OR patient education/ OR regimen:.tw.) AND (intervention: OR outcome:).tw. AND (medicat:.tw. OR drug therapy/)) NOT ((qualitative OR retrospective OR mice OR rat OR rats).tw. OR editorial.pt. OR letter.pt. OR comment.pt.) NOT (animals NOT humans).sh.
- 3. ((exp hypertension/ OR (blood adj pressure).ti. OR hypertens\$.ti OR/1-3))**

**CINAHL** search filters used in this update using the EBSCO interface:

1. MH patient compliance+ OR TI "patient compliance" OR AB "patient compliance" OR TI "patient adherence" OR AB "patient adherence" OR TI "medication compliance" OR AB "medication compliance" OR TI "medication adherence" OR AB "medication adherence" NOT PT editorial or PT letter or TI qualitative or AB qualitative or TI retrospective or AB retrospective or TI mice or AB mice or TI rat or AB rat or TI rats or AB rats (limited by Clinical Queries therapy sensitive search filter and date - 2007 to 2012 )
2. MH patient compliance OR MH medication compliance OR MH patient dropouts OR MH treatment refusal OR MH patient education OR TI psychotherapy OR AB psychotherapy AND TX ( (random\* OR control\* ) ) AND TX ( (medicat\* OR drug therapy) ) NOT PT

editorial or PT letter or TI qualitative or AB qualitative or TI retrospective or AB retrospective or TI mice or AB mice or TI rat or AB rat or TI rats or AB rats

**3. MH hypertension OR TI hypertension OR AB hypertension OR MH “blood pressure” OR TI “blood pressure” OR AB “blood pressure” NOT PT editorial or PT letter or TI qualitative or AB qualitative or TI retrospective or AB retrospective or TI mice or AB mice or TI rat or AB rat or TI rats or AB rats**

**EMBASE** search filter used in this update using the Ovid interface: (random: or control:).mp. AND (patient compliance or patient dropouts or illness behavior or psychotherapy or treatment refusal or patient education or regimen:).mp. AND(intervention: or outcome: or treatment outcome).mp. AND(medicat: or drug therapy).mp. AND (clinical trial or controlled study or randomized controlled trial).mp. **AND (hypertension or hypertens\$ or blood pressure).mp.**

**PsycINFO** search filter used in this update using the Ovid interface: (((control: or random:).tw. or exp treatment/) and (adherence or compliance or noncompliance or dropouts or patient education).mp. and (drug therapy or drug or medicat: or treatment or regimen).mp. and (intervention or outcomes or treatment outcomes).mp.) not (qualitative or retrospective or mice or rat or rats).tw. **AND (hypertension or hypertens\$ or blood pressure).mp.**

**The Cochrane Library** search filter used in this update

(<http://onlinelibrary.wiley.com/cochranelibrary/search/>):

((random\*) AND (complian\* or adheren\* or pharmacotherapy or regimen\* or educat\*) AND (medicat\*) **AND (hypertension or hypertens\$ or blood pressure)** (Note: Searched using all

text tag; Search by product: Cochrane Database of Systematic Reviews, DARE (Other Reviews), Central; Search by record: all)

**Sociological Abstracts** search filter used in this update using the ProQuest interface (<http://search.proquest.com/socabs/advanced>): ((patient or treatment or dropouts) AND (clinical trials or control) AND (drugs or medicine or medication) **AND (hypertension or hypertens\$ or blood pressure)**) (Searched using all fields; all(medication) retrieves su(medication adherence))

**ClinicalTrials.gov** search filter used in this update (<http://clinicaltrials.gov/ct2/search/advanced>): “patient compliance” OR “patient adherence” OR “medication compliance” OR “medication adherence” **AND “hypertension” OR “blood pressure”** | Closed Studies | Studies With Results |

**International Clinical Trials Registry Platform** search filter used in this update (<http://apps.who.int/trialsearch/AdvSearch.aspx>): patient compliance or patient adherence or medication compliance or medication adherence **and hypertension or blood pressure** (Note: recruitment status all used)

### Appendix III: Data extraction form

1. Title of article
2. Citation
3. Database ID
4. Author abstract
5. Study setting
6. Clinical problem
7. Participant inclusion/exclusion criteria
  - a. Number randomised to intervention group
  - b. Number randomised to control group
8. Intervention (Repeated for each intervention)
  - a. Complete description of intervention
    - i. Heading - Nature of intervention: [textbox]
    - ii. Heading- Who did what to whom: [ textbox]
    - iii. Heading - Number of sessions: [ textbox]
    - iv. Heading - Duration of follow up: [ textbox]
    - v. Heading - Intensity of intervention (if mentioned): [ textbox]
  - b. Based on a), who received the adherence intervention?
    - i. Patient
    - ii. Caregivers
    - iii. Patients' family or friends
    - iv. Research staff
    - v. Other [typed answer \_\_\_\_\_]
  - c. Based on the description in a) what type(s) of intervention(s) was (were) tested in the intervention group (check all that apply)?
    - i. Increased supervision from physician prescriber (e.g., more frequent visits, phone calls)
    - ii. Increased supervision from nurse
    - iii. Increased supervision by pharmacist
    - iv. Increase supervision by other provider  
[Typed answer: \_\_\_\_\_]

- v. Additional medication instructions for patients in the intervention group (e.g., verbal, written, or visual material)
- vi. Additional instructions/ education for patients in the intervention group on their disease or adherence (e.g., verbal, written, or visual material)
- vii. Patient counseling (e.g., about the target disease, importance of therapy, compliance with therapy, possible side-effects, patient empowerment, couple-focused therapy to increase social support)
- viii. Automated patient monitoring and counseling (telephone, cell phone, or computer assisted)
- ix. Manual telephone follow-up
- x. Family/social intervention (e.g., involvement of family members/significant others in the intervention)
- xi. Increased convenience of care (e.g., provision at the workplace or at home)
- xii. Simplified dosing (i.e. changing frequency of medication use)
- xiii. Increased self-care (involving patients more in their care, e.g., through self-monitoring their blood pressure)
- xiv. Reminders (e.g., programmed medication devices)
- xv. Special pill packaging (e.g., calendar packs)
- xvi. Dose-dispensing units of medication and medication charts
- xvii. Appointment and prescription fill reminders
- xviii. Reinforcements or rewards for improved adherence
- xix. Reinforcement or rewards for improved treatment response (e.g., reduced frequency of visits and partial payment for blood pressure monitoring equipment)
- xx. Different medication formulations (e.g., tablet vs. syrup)
- xxi. Crisis intervention conducted when necessary (e.g., for attempted suicide, aggressive and destructive behaviour)
- xxii. Direct observation of treatments (DOTS) by health workers or family members
- xxiii. Lay health mentoring
- xxiv. Augmented pharmacy services
- xxv. Psychological therapy (e.g., cognitive behaviour therapy, multisystemic therapy)

- xxvi. Mailed communications
- xxvii. Group meetings
- xxviii. Social media (eg, Twitter, Facebook)
- xxix. Other(s) [\_\_\_\_\_]

d. Provide a description of the Control procedure [cut and paste text from the article if possible:\_\_\_\_\_

- i. Heading - Nature of intervention: [textbox]
- ii. Heading- Who did what to whom: [ textbox]
- iii. Heading - Number of sessions: [ textbox]
- iv. Heading - Duration of follow up: [ textbox]
- v. Heading - Intensity of intervention (if mentioned): [ textbox]

e. Based on the description of the Control procedure, did Control participants receive attention or intervention beyond usual care with the intention of offsetting the additional attention received by Intervention participants? Yes / No / Unclear

9. What was/were the measures of adherence?

10. What was/were the clinical health outcomes?

11. Outcomes:

1. Results for adherence outcomes

a) Results for adherence outcomes - extract all adherence outcomes in detail and their variance for each study group, as well as levels of statistical significance for differences between study groups.

b) Was there a statistically significant effect on adherence outcomes?

Yes / No / Unsure

2. Results for clinical health outcomes

a) Results for clinical health outcomes - extract all clinical outcomes in detail and their variance for each study group, as well as levels of statistical significance for differences between study groups.

b) Was there a statistically significant effect on clinical health outcomes?

Yes / No / Unsure

### Appendix IV: Coding interventions with the TDF

Study	Description of intervention	Domain	Construct	Determinant	Description of control	Domain	Construct	Determinant
Amado (2011)	Patients in the Intervention Group (IG) had 4 visits with <i>pecially trained nurses</i> who used standardized guidelines and who had attended a 10-hour workshop that focused on the antihypertensive medications. Each visit lasted for an average of 15 minutes. Nurses provided information on the disease, healthy lifestyle habits, advice on medication (mechanisms of action, dosage, what to do if a pill is missed, adverse effects). This information was personalized to the needs of the patient. Leaflets were provided that allowed the development of a personalised therapeutic plan; general health messages aimed at promoting the good utilisation of drugs. Schedule sheets with the treatment plan were provided, which contained information on the prescribed drugs and dosage schedule as well as basic advice on how to maximize the treatment schedule. The sheets were provided to reinforce the nurse's verbal instructions.	Memory, attention and decision processes  Knowledge  Beliefs about consequences  Behavioural regulation  Social influences  Environmental context and resources  Memory, attention and decision processes	Attention  Knowledge Procedural knowledge  Outcome expectancies  Self-monitoring Action planning  Social pressure Social support  Material resources`  Attention	Intervention (focuses attention)  Nurses provided information  Advice on medication  Schedule sheets  Nurse visit  Leaflets and schedule sheets  Nurse visits (focus attention)	Usual care	None identified		
Baird (1984)	Betaloc Durules 200 mg every morning (0600 to 0900 hours)	Memory, attention and decision processes  Environmental context and resources	Attention  Barriers and facilitators	Intervention (focuses attention)  Once daily pill	Betaloc tablets 100 mg in the morning (0600 to 0900 hours), and in the evening (12 hours later)	None identified		

		Memory, attention and decision processes	Cognitive overload	Simplification of dose				
Becker (1986)	Patients in the IG received all their medications in the special packaging format (all pills taken together were packaged in a single plastic blister sealed with a foil backing on which was printed the day of the week and the time of day at which each medication was to be taken). All medications for both groups were provided free of charge to ensure that all patients would receive their medications	Memory, attention and decision processes  Environmental context and resources  Memory, attention and decision processes	Attention  Barriers and facilitators  Cognitive overload	Intervention (focuses attention)  Once daily pill  Simplification of dose	Patients in the control group received all of their antihypertensive medications in the traditional pill vials (separate vials for each pill that were labeled with the drug name, the dosage, the medication instructions, and the physician's name). All medications for both groups were provided free of charge to ensure that all patients would receive their medications	Environmental context and resources	Barriers and facilitators	Free medication
Dusing (2009)	Physician dialogue - possible causal factors for high BP, risks of hypertension and necessity for long term medical treatment. Set of supportive measures - it was up to the patients to select the tools they would like to use on an individual basis. For the patient: (a) 24-hour timer: the timer can be set to an individual time and provides an acoustic signal every 24 hours at this point of time; (b) Set of 10 reminding stickers to be positioned at prominent places at home (e.g. refrigerator and bathroom mirror); (c) Information brochure for patients with hypertension published by the German Hypertension Society; (d) Information letter for the patient; (e) Information letter the patient can give to next of kin to receive support or his therapy (e.g. spouse reminding of drug intake); (f) Home BP measurement device; (g) Booklet to document home BP measurements	Memory, attention and decision processes  Social influence  Knowledge  Beliefs about consequences  Environmental context and resources  Memory, attention and decision	Attention  Social support Social pressure  Knowledge  Beliefs Outcome expectancies  Material resources Barriers and facilitators  Memory	Intervention (focuses attention)  Physician dialogue  Physician dialogue Brochure Information letter  Physician dialogue  Supportive measures Timer and stickers  Timer and stickers	Usual care	None identified		

		processes							
		Social influence	Social support	Letter for next of kin					
		Behavioural regulation	Self-monitoring	Home BP device and booklet					
Friedberg 2015	<p>All participants received standard information about hypertension and its treatment at enrollment.</p> <p><b>Stage matched intervention</b>  Patients in SMI received tailored monthly phone counseling for exercise, diet, and medications based on the current stage of change, using a computer-based intervention manual. During each call (≈30 minutes), the stage of change for adherence to diet, medication, and exercise was assessed separately using the validated stage of change questions and tailored counseling based on this assessment. The stages of change were precontemplation or no plans to adhere in &lt;6 months; contemplation or plans to adhere in 1 to 6 months; preparation or plans to adhere within 1 month; action or adherence for &lt;6 months; and maintenance or adherence for ≥6 months. Patients were considered adherent to diet if they reported eating the appropriate diet for hypertension (low in salt and fat with fruits, vegetables, and low-or nonfat dairy products) ≥6 days/wk. Specific recommendations, such as trimming visible fat from meat and asking for sauces on the side in restaurants were provided each month, and any additional dietary questions were answered. The intervention was tailored to target personal barriers and brainstorm solutions.  Medication adherence was defined as the self-report of taking BP medications as prescribed for ≥6 days/wk. Although refill compliance was measured, the stage of</p>	<p>Knowledge</p> <p>Beliefs about consequence</p> <p>Memory, attention and decision processes</p> <p>Social influences</p> <p>Behavioural regulation</p> <p>Intentions</p>	<p>Knowledge</p> <p>Characteristics of outcome expectancies</p> <p>Attention</p> <p>Social support</p> <p>Self monitoring</p> <p>Stages of change model</p>	<p>Standard information</p> <p>Information about treatment</p> <p>Intervention (focuses attention)</p> <p>Phone counselling</p> <p>Phone assessment</p> <p>Stages of change</p>		<p>All participants received standard information about hypertension and its treatment at enrollment.</p>	<p>Knowledge</p> <p>Beliefs about consequence</p>	<p>Knowledge</p> <p>Characteristics of outcome expectancies</p>	<p>Standard information</p> <p>Information about treatment</p>



Friedman (1996)	<p>The IG received regular medical care plus the telephone-linked computer system (TLC). TLC is an interactive computer-based telecommunications system that converses with patients in their homes, using computer-controlled speech, between office visits to their physicians. The intervention patients would call the TLC on a weekly basis. Before calling, subjects would record their own blood pressure using an automated sphygmomanometer with a digital readout. During the conversation they reported 1. BP 2. understanding of medication regime 3. adherence 4. symptoms of side effects. The TLC would provide education and motivational counseling to improve medication adherence. The TLC then transmitted the reported information to the subject's physician.</p>	<p>Memory, attention and decision processes</p> <p>Environmental context and resources</p> <p>Memory, attention and decision processes</p> <p>Knowledge</p> <p>Behavioural regulation</p> <p>Beliefs about consequences</p> <p>Social influences</p>	<p>Attention</p> <p>Material resource</p> <p>Attention</p> <p>Knowledge</p> <p>Self-monitoring</p> <p>Beliefs Outcome expectancies</p> <p>Social pressure</p>	<p>Intervention (focuses attention)</p> <p>TLC</p> <p>Calling the TLC (focuses attention)</p> <p>Education and motivational counselling</p> <p>Recording and reporting BP measures</p> <p>Education and motivational counselling</p> <p>Reported information to physician</p>	Usual care	None identified		
Girvin (1999)	Enalapril 20 mg once daily	<p>Memory, attention and decision processes</p> <p>Environmental context and resources</p> <p>Memory, attention and decision processes</p>	<p>Attention</p> <p>Barriers and facilitators</p> <p>Cognitive overload</p>	<p>Intervention (focuses attention)</p> <p>Once daily pill</p> <p>Simplification of dose</p>	Enalapril 10 mg twice daily.	None identified		

Greer 2015	<p>The culturally tailored intervention consisted of six 90-minute sessions offered once a week for 6 weeks to groups of 8 to 12 women. The groups were led by the author (DBG) who has a background in cardiovascular nursing. The 14 standards derived from the Office of Minority Health Culturally Linguistic Appropriate Standards were used as a framework. Key Culturally Linguistic Appropriate Standards followed included race concordance of the RAs and author (DBG), culturally tailored educational materials that were easy to understand, setting in the AA community, culturally appropriate language respectful of AAs, and an ongoing assessment of the intervention through participant feedback.</p> <p>Terms known to participants were used to discuss pressure medicine, fluid pills, use of pickle juice and other folk remedies to lower high blood, and hidden sources of salt. Participants were given a blank family tree to outline ancestors and descendants, and discussions on medication adherence were tied to ancestors and descendants (and their medical histories). Participants were asked to discuss managing medication adherence, adverse effects, and ways of coping with HTN. Content on physical activity, weight management, stroke prevention, and target organ damage was also included.</p> <p>Each session began with prayer and ended with a unity circle and prayer, in which all persons joined hands while 1 person said a prayer. The gospel song Never Would Have Made It<sup>18</sup> was also played at each session. Content was delivered through lectures, videos, pictures, and handouts in an easy-to-read format. The average Flesch-Kincaid<sup>19</sup> reading level of the materials was grade level 8.5. Of the 60 participants, 11.6% (n</p>	<p>Memory, attention and decision processes</p> <p>Social influences</p> <p>Environmental context &amp; resources</p> <p>Environmental context &amp; resources</p> <p>Knowledge</p>	<p>Attention</p> <p>Social support</p> <p>Person x environment interaction</p> <p>Resources</p> <p>Knowledge</p>	<p>Intervention (focuses attention)</p> <p>Author</p> <p>Culturally tailored</p> <p>Educational materials</p> <p>Content</p>	Wait list control	None identified		
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	<p>= 7) had less than a high school education.</p> <p>The curriculum included materials from the American Heart Association and the National Heart Lung and Blood Institute. Participants were provided with a notebook of materials from the American Heart Association, the National Heart Lung and Blood Institute, and The Power to End Stroke (PTES) Campaign. The PTES DVD,20 in which laypersons and key celebrities such as the late Yolanda King discuss HBP and stroke prevention, was also shown to participants. Additional content included scriptures on health and wellness, information for increasing healthcare access and resources, the importance of social support, and attitudes and cultural beliefs about HBP.</p>							
Haynes (1976)	<p>Patients were given a home BP monitor, a daily pill and blood pressure chart and asked to record BP and adherence. Tailoring (telling patients to place medications in places of rituals), monetary reward for low BP reading every fortnight, verbal praise for periods of compliance, reasons for every missed pill identified, encouragement to do better if there was no drop in BP or good compliance</p>	<p>Memory, attention and decision processes</p> <p>Behavioural regulation</p> <p>Environmental context and resources</p> <p>Reinforcement</p> <p>Social influence</p>	<p>Attention</p> <p>Self-monitoring</p> <p>Material resource</p> <p>Barriers and facilitators</p> <p>Rewards</p> <p>Social support</p>	<p>Intervention (focuses attention)</p> <p>Self BP recording</p> <p>Home BP kit</p> <p>Places of rituals</p> <p>Monetary reward</p> <p>Verbal praise and encouragement</p>		Usual care	None identified	

Hosseinasab 2014	<p>Patients received a wrist blood pressure measurement device (SHB-200w, P/N 323101356; Samsung C&amp;T, Seoul, Korea). They were instructed how to use the device and document their measurements in a logbook. They were advised to measure their blood pressure once daily at a specific time every day. The logbook was checked at each visit by the investigator and was collected at the final visit for data analysis.</p>	<p>Memory, attention and decision processes</p> <p>Environmental context and resources</p> <p>Behavioural regulation</p> <p>Knowledge</p> <p>Social influences</p>	<p>Attention</p> <p>Resources</p> <p>Self-monitoring</p> <p>Procedural knowledge</p> <p>Social support</p>	<p>Intervention (focuses attention)</p> <p>Device</p> <p>Log book</p> <p>Instructed to use device</p> <p>Logbook checked</p>	Patients received usual care as suggested by the physician.			
Johnson (1978)	<p><b>Intervention 1</b> Self recording and monthly home visits Received a BP kit and instructions in recording. Patients were to keep charts of their daily BP readings and were instructed to bring these charts to their physician at each appointment. Had their BP measured at home every 4 weeks and results were reported to both the patient and the physician.</p> <p><b>Intervention 2</b> Received a BP kit and instructions in recording. Patients were to keep charts of their daily BP readings and were instructed to bring these charts to their physician at each appointment.</p> <p><b>Intervention 3</b> Monthly home visits Had their BP measured at home every 4 weeks and results were reported to both the patient and the physician.</p>	<p><b>1.</b> Memory, attention and decision processes</p> <p>Environmental context and resources</p> <p>Behavioural regulation</p> <p>Social influences</p> <p>Social influences</p> <p>Memory, attention and decision processes</p> <p><b>2.</b> Memory, attention and decision processes</p> <p>Environmental context and</p>	<p>Attention</p> <p>Material resource</p> <p>Self-monitoring</p> <p>Social support</p> <p>Social pressure</p> <p>Attention</p> <p>Attention</p> <p>Material resource</p>	<p>Intervention (focuses attention)</p> <p>Home BP kit</p> <p>Self BP recording</p> <p>Home visits</p> <p>Results reported to physician</p> <p>Monthly visit (focuses attention)</p> <p>Intervention (focuses attention)</p> <p>Home BP kit</p>	Usual care	None identified		

		resources						
		Behavioural regulation	Self-monitoring	Self BP recording				
		<b>3.</b> Memory, attention and decision processes	Attention	Intervention (focuses attention)				
		Social influences	Social support	Home visits				
		Social influences	Social pressure	Results reported to physician				
Margolius (2012)	Home monitoring of BP. Health coaches made weekly telephone calls to participants in both study arms to discuss overall well-being, adherence to action plans, and blood pressure values. Clinicians of patients in the home-titration arm completed an algorithm of antihypertensive medication adjustments. Patients in the home-titration arm who reported blood pressure greater than 140 mmHg systolic or greater than 90 mmHg diastolic and excellent medication adherence could choose to increase their antihypertensive medication regimen according to the algorithm without a clinician appointment. In those cases, health coaches notified a physician investigator to fax the prescription to the pharmacy. Clinicians were notified of medication changes by e-mail, and health coaches entered the change in the electronic health record.	Memory, attention and decision processes	Attention	Intervention (focuses attention)	Home monitoring and health coaching (health coaches made weekly telephone calls to participants in both study arms to discuss overall well-being, adherence to action plans, and blood pressure values.)	Memory, attention and decision processes	Attention	Intervention (focuses attention)
		Environmental context and resources	Material resource	Home BP kit		Environmental context and resources	Material resource	Home BP kit
		Behavioural regulation	Self-monitoring	Self BP recording		Behavioural regulation	Self-monitoring	Self BP recording
		Social influence	Social support	Weekly calls		Social influence	Social support	Weekly calls
		Memory, attention and decision processes	Attention	Weekly phonecalls (focus attention)		Memory, attention and decision processes	Attention	Weekly phonecalls (focus attention)
Marquez Contreras (2005)	<b>Intervention 1</b> Participants allocated to the telephone intervention group (TIG) received a controlled intervention in the form of 3 telephone calls: the first 15 days after the inclusion visit; the second and third being one week after visits 3 and 4. The	<b>1.</b> Memory, attention and decision processes	Attention	Intervention (focuses attention)	Usual care	None identified		
		Memory,	Attention	Phone calls (focus				

	<p>telephone intervention was made by 2 expert nurses in this type of interventions. During the calls to patients in this group, the patients were reminded of scheduled visits and asked about the name, dosage, and timing of their antihypertensive medication, and the number of remaining tablets. Patients were informed, according to the number of tablets in their possession, if they had good or poor compliance. In the event of good compliance, the patients were congratulated and encouraged to continue adhering to therapy. In the event of noncompliance, the patients were encouraged to comply, and the associated benefits were explained.</p> <p><b>Intervention 2</b></p> <p>For participants who were allocated to the mail intervention group (MIG), they received 3 mailed communications at home: the first 15 days after the inclusion visits; the second and third, being one week after visits 3 and 4; in order to promote compliance through health education in hypertension, reinforce compliance, and remind the subjects of the scheduled visits. The mailed messages included information about the following hypertension aspects: what is hypertension?; diagnosis of hypertension; symptoms; related risk factors; why is necessary to treat the hypertension?; what is the hypertension treatment?; and information about the correct taking of medication.</p>	<p>attention and decision processes</p> <p>Social influence</p> <p>Reinforcement</p> <p>Behavioural regulation</p> <p>Beliefs about consequences</p> <p><b>2.</b> Memory, attention and decision processes</p> <p>Environmental context and resources</p> <p>Memory, attention and decision processes</p> <p>Knowledge</p> <p>Beliefs about consequences</p>	<p>Social support</p> <p>Reward</p> <p>Feedback on behaviour</p> <p>Outcome expectancies</p> <p>Attention</p> <p>Material resource</p> <p>Attention</p> <p>Knowledge</p> <p>Outcome expectancies</p>	<p>attention)</p> <p>Telephone calls by expert nurses</p> <p>Congratulated and encouraged</p> <p>Informed about compliance</p> <p>Associated benefits were explained</p> <p>Intervention (focus attention)</p> <p>Letter</p> <p>3 letters (focus attention)</p> <p>Health education in hypertension</p> <p>Why it is important to treat hypertension</p>				
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Marquez Contreras (2006)	Patients in this intervention, apart from receiving the usual care, also received an OMRON automatic monitor for home blood pressure measurement (HBPM). The patients received a kit in their home containing the monitor, an instruction manual, a summary of the functions, and a card on which to note the measurements. They were advised to follow the HBPM program, which consisted of measuring the BP 3 days a week (Tuesdays, Thursdays, and Saturdays), twice before breakfast (0800 to 1000 hours) and twice before supper (2000 to 2200 hours) and record these results on the card (4 times a day). The patients received a phone call to explain how to use the monitor and follow the HBPM program.	Memory, attention and decision processes  Environmental context and resources  Behavioural regulation  Memory, attention and decision processes	Attention  Material resource  Self-monitoring  Attention	Intervention (focuses attention)  Home BP kit  Self BP recording  Phone call (focuses attention)	Usual care	None identified		
Matsumura (2012)	The intervention was a combination pill instead of multiple pills. Patients assigned to the intervention group received a combination pill (losartan 50mg/hydrochlorothiazide 12.5 mg).	Memory, attention and decision processes  Environmental context and resources  Memory, attention and decision processes	Attention  Barriers and facilitators  Cognitive overload	Intervention (focuses attention)  Once daily pill  Simplification of dose	Control patients were provided with an angiotensin receptor blocker and a diuretic.	None identified		
Morgado (2011)	Pharmaceutical care: baseline visit and 2 follow up visits (optional additional visits). At each visit the pharmacist conducted a thorough interview of the patient, identified problems leading to poor BP control, provided patient education (hypertension education, BP self-monitoring recommendations, goal BP to achieve, lifestyle education and counselling, medication education and counselling tips to enhance adherence) and presented recommendations to the physician regarding changes in drug therapy. Patients were also provided with	Memory, attention and decision processes  Social influences  Memory, attention and decision processes  Knowledge	Attention  Social support  Attention  Knowledge	Intervention (focuses attention)  Pharmacist visits  Follow up visits (focus attention)  Patient education	Usual care	None identified		

	written educational material about hypertension and possible complications, as well as healthy lifestyle practices. Patients were encouraged to bring all empty blisters and boxes of meds to clinic visits for recycling and verifying compliance.	Beliefs about consequences Environmental context and resources Goals Behavioural regulation	Outcome expectancies Material resources Goal setting Self monitoring Feedback	Medication education Written educational material Goal BP to achieve Self-monitoring recommendation Empty blisters				
Ogedegbe (2012)	Patients randomized to the Positive Affect (PA) intervention group were given the same workbook as those in the PE group but with an additional chapter that addresses the benefits of positive moments in overcoming obstacles to medication adherence. Also, these patients received 2 forms of PA during bimonthly telephone calls. First, they were asked to identify small things in their lives that invoke positive feelings in them and were then instructed to incorporate these positive thoughts into their daily routine. The positive thoughts were further reinforced during subsequent bimonthly telephone calls. Second, the patients received unexpected small gifts mailed to them before each telephone call. This strategy was based on the potential of the receipt of unexpected gifts to induce positive feelings. For self affirmation induction, the patients were asked to remember their core values and proud moments in their lives whenever they encounter situations that make it difficult for them to take their medications	Memory, attention and decision processes Environmental context and resources Knowledge Behavioural regulation Goals Memory, attention and decision processes Social influences Emotion	Attention Material resource Knowledge Action planning Goal setting Attention Social pressure Affect	Intervention (focuses attention) Workbook Enhance patients knowledge Behavioural contract Support goal-setting Telephone calls (focus attention) Behavioural contract PA intervention	Patient Education (PE) control group received a culturally tailored educational workbook designed (1) to enhance patients' knowledge about hypertension, (2) to improve self management behaviors, and (3) to support goal-setting. On receipt of the workbook, trained Research Assistants (RAs) reviewed each chapter with the patients and then asked them to sign a behavioral contract that asked them to make a commitment to taking their medications as prescribed. Subsequent to this session, each patient received bimonthly telephone calls, during which the RAs assessed the patient's behavioral contract and confidence to take their medications as prescribed. These assessments served as the basis for reviewing and counseling the patient on perceived barriers to medication adherence.	Memory, attention and decision processes Environmental context and resources Knowledge Behavioural regulation Goals Memory, attention and decision processes Social influences	Attention Material resource Knowledge Action planning Goal setting Attention Social pressure	Intervention (focuses attention) Workbook Enhance patients knowledge Behavioural contract Support goal-setting Telephone calls (focus attention) Behavioural contract

Ogedegbe 2014	Patients at the IC sites received: (1) four modules of interactive computerized patient education focused on the causes, complications and treatment of HTN, expected medication side effects, and methods for adoption of healthy lifestyle behaviors; (2) six behavioral lifestyle telephone/group counseling sessions; and (3) free validated automated home BP monitors (Dunedin, FL: Microlife USA, Inc., Model BP 3AC1-1 PC); and encouraged to record their weekly BP readings (twice daily, three days a week) in a diary and bring it to each study visit. The PCCs received monthly onsite CME based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), <sup>11</sup> hypertension case rounds, and quarterly chart audits of their patients' office BP readings. They were also provided quarterly feedback on the values of their patients' home BP readings, which were obtained from the patients' diaries.	Memory, attention and decision processes Knowledge Beliefs about consequence Social influences Environmental context and resources Behavioural regulation	Attention Knowledge Outcome expectancies Social support Resources Self monitoring	Intervention (focuses attention) Patient education Treatment of HTN Counselling sessions BP device Diary	Patients at the enhanced UC sites received a single hypertension patient education session plus printed versions of the NHLBI patient education material ' <i>Your Guide to Lowering Blood Pressure</i> ' and ' <i>Facts about the DASH Eating Plan</i> ', while the PCCs received print versions of JNC-7 guidelines.	Memory, attention and decision processes Knowledge Material context and resources	Attention Knowledge Resources	Intervention (focuses attention) Education session Education material
Rudd (2004)	Patients were given an automated BP device. The intervention consisted of the nurse care manager conducting baseline counseling on the correct use of the automated BP device, regular return of the automatically printed BP reports, tips for enhancing drug adherence, and recognition of potential drug side effects. The nurse initiated follow-up phone contacts at 1 week and at 1, 2, and 4 months that averaged 10 minutes in duration. During the phone calls, the nurse asked the patients about each medication dosage and any problems experienced since the previous contact. Patients were encouraged to telephone anytime during regular hours with questions or concerns. The nurse care manager contacted physicians to obtain permission to initiate any new BP drug but did not contact physicians regarding	Memory, attention and decision processes Environmental context and resources Social influences Knowledge Behavioural regulation Memory, attention and decision	Attention Material resources Social support Knowledge Self-monitoring Attention	Intervention (focuses attention) Automated BP device Phone calls from nurse Tips for enhancing drug adherence Use of BP device Phone calls (focus attention)	Usual care	None identified		

	changes in medication dosage.	processes						
Sackett (1975)	<p><b>Intervention 1</b> Augmented convenience: patients saw the work doctor during working hours and while on full pay.</p> <p><b>Intervention 2</b> Mastery learning: patients were given an educational programme designed to give them the facts about hypertension, its effects upon target organs and life expectancy, the benefits of meds, need for compliance with meds and some simple reminders for pill taking. Information was supplied on a slide-audiotape format and a booklet. A patient educator periodically checked what patients had remembered and re-emphasised insufficiently mastered information.</p>	<p><b>1.</b> Memory, attention and decision processes</p> <p>Environmental context and resources</p> <p><b>2.</b> Memory, attention and decision processes</p> <p>Knowledge</p> <p>Beliefs about consequences</p> <p>Memory, attention and decision processes</p> <p>Environmental context and resources</p>	<p>Attention</p> <p>Barriers and facilitators</p> <p>Attention</p> <p>Knowledge</p> <p>Outcome expectancies</p> <p>Memory</p> <p>Material resource</p>	<p>Intervention (focuses attention)</p> <p>Work doctor</p> <p>Intervention (focuses attention)</p> <p>Facts about HTN</p> <p>Effects of HTN</p> <p>Simple reminders</p> <p>Audiotape and booklet</p>		Usual care	None identified	
Schroeder (2005)	<p>Patients in the intervention group received, in addition to usual care, a nurse-led adherence support session lasting a maximum of 20 minutes, followed by a shorter reinforcement session (10 minutes) 2 months later. The intervention was aimed to provide an opportunity for patients to talk about any problems with their blood pressure-lowering medication. Practice nurses investigated whether patients understood their diagnosis and agreed with the treatment process. They also addressed patient concerns with their medication and to agree to tailored strategies to</p>	<p>Memory, attention and decision processes</p> <p>Social influence</p> <p>Beliefs about consequences</p> <p>Memory, attention and decision</p>	<p>Attention</p> <p>Social support</p> <p>Outcome expectancies</p> <p>Attention</p>	<p>Intervention (focuses attention)</p> <p>Nurse-led support session</p> <p>Patients understood their diagnosis</p> <p>Reinforcement session (focuses attention)</p>		The control group received standard care delivered at their respective practices, apart from blood pressure checks at similar intervals as the participants in the intervention group.	None identified	

	resolve any medication problems.	processes						
Stewart 2014	<p>During the baseline visit to the pharmacy, the pharmacist measured the patient's BP using a digital BP monitor.</p> <p>PCG participants received a package of interventions from the pharmacist for enhancing their antihypertensive medication adherence, which included the following:</p> <ul style="list-style-type: none"> <li>• A home BP monitor (Omron_HEM-790IT) with the capacity to store and download BP readings to be used for discussion at three- and 6- month follow-ups;</li> <li>• Training by the pharmacist on self-monitoring of BP;</li> <li>• Motivational interviewing and education by the pharmacist to help patients improve their medication adherence and achieve target BP;</li> <li>• Pharmacy-based medicines review to identify and resolve, where necessary, possible medication-induced hypertension (e.g. due to non-steroidal anti-inflammatory drugs, cold preparations, complementary medicines);</li> <li>• Pharmacist-initiated dose administration aid (DAA), home-based medicines review and/or patient medication list, where necessary;</li> <li>• Referral to a GP at the pharmacist's discretion; and</li> <li>• Refill reminders (by SMS, telephone or mail), if they so chose, from their pharmacist 3 days before their antihypertensive medication was due to run out.</li> </ul> <p>Pharmacist Care Group participants returned to the pharmacy at 3 months for review and action based on the downloaded home BP measures.</p>	<p>Memory, attention and decision processes</p> <p>Environmental context and resources</p> <p>Behavioural regulation</p> <p>Knowledge</p> <p>Social influences</p> <p>Beliefs about consequence</p> <p>Goals</p> <p>Environmental context and resources</p> <p>Memory, attention and decision processes</p>	<p>Attention</p> <p>Resources</p> <p>Self-monitoring</p> <p>Procedural knowledge</p> <p>Social support</p> <p>Outcome expectancies</p> <p>Goal setting</p> <p>Resources</p> <p>Memory</p>	<p>Intervention (focuses attention)</p> <p>Package of interventions</p> <p>Home BP device</p> <p>Training by pharmacist</p> <p>Pharmacist</p> <p>Motivational interviewing</p> <p>Motivational interviewing DAA</p> <p>Refill reminders</p>	<p>During the baseline visit to the pharmacy, the pharmacist measured the patient's BP using a digital BP monitor.</p> <p>UCG participants continued to receive routine care.</p> <p>Measures performed at baseline were repeated for both UCG and PCG patients at their 6-month visit to the pharmacy. Following final measurements, each UCG participant was eligible to receive the same package of interventions offered to the PCG at baseline.</p>			

	Measures performed at baseline were repeated for both UCG and PCG patients at their 6-month visit to the pharmacy. Following final measurements, each UCG participant was eligible to receive the same package of interventions offered to the PCG at baseline.							
Svarstad 2013	<p>In addition to the materials given to control participants, TEAM participants were invited to participate in the 6-month intervention. After receiving a list of eligible patients, intervention teams attempted to contact and invite patients to activate the intervention by completing a team intake and initial pharmacist consultation. Pharmacists attempted to complete one team intake and five follow-up visits per patient and to fax an introductory letter and feedback to physicians if patients did not achieve blood pressure control by month 3 (or earlier if necessary). The intervention was based largely on the Health Collaboration Model and involved several unique strategies.<sup>9</sup></p> <p>First, we developed and provided clinical toolkits for pharmacists and technicians. These user-friendly toolkits included modified Brief Medication Questionnaires (BMQs)<sup>26</sup> and other patient self-report tools for easy identification and monthly assessment of the 'core' barriers targeted in this trial (patient misunderstandings of blood pressure goals and regimen; patient doubts or concerns about drug efficacy, adverse effects, and long-term effects; and difficulties remembering, paying, or refilling on time). Pharmacy technicians asked patients to complete these self-report tools in the waiting area before they met with pharmacists, saving time for staff and patients. In addition to patient self-report tools, the clinical toolkits included simple algorithms for</p>	<p>Memory, attention and decision processes</p> <p>Knowledge</p> <p>Environmental context and resources</p> <p>Beliefs about consequence</p> <p>Environmental context and resources</p> <p>Goals</p>	<p>Attention</p> <p>Knowledge</p> <p>Resources</p> <p>Outcome expectancies</p> <p>Resources</p> <p>Goal setting</p>	<p>Intervention (focuses attention)</p> <p>Patient information Guide and cards</p> <p>Instructions</p> <p>Clinical toolkits</p> <p>BP goals</p>	<p>Control participants received patient information only, including a 14-page guide for lowering blood pressure, pamphlet about hypertension in black patients, cards showing their blood pressure at baseline and follow-up interviews, and instructions to seek immediate medical care for a blood pressure value greater than 210/115 mm Hg at 6- or 12-month follow-up. Primary care physicians received an introductory letter; Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). guidelines<sup>25</sup>; and names of eligible patients. Pharmacy staff received a study description, posters, interest forms, JNC-7 guidelines, and no additional tools or training.</p>	<p>Memory, attention and decision processes</p> <p>Knowledge</p> <p>Environmental context and resources</p> <p>Beliefs about consequences</p>	<p>Attention</p> <p>Knowledge</p> <p>Resources</p> <p>Outcome expectancies</p>	<p>Intervention (focuses attention)</p> <p>Patient information Guide and cards</p> <p>Instructions</p>

	<p>addressing identified barriers, one-page checklists for documenting and tracking barriers and interventions, structured tools for faxing feedback to physicians (if needed), and validated blood pressure monitors and portable furniture for a semiprivate blood pressure station.</p> <p>Second, we developed and provided one take-home toolkit for each patient. This patient toolkit included a wallet card for recording blood pressure readings, 7-day medication box for remembering doses, easy-to-read leaflets for increasing patient awareness and involvement in the TEAM program, and a pedometer for reinforcing lifestyle change. Pharmacists used various tools to facilitate two-way communication during the initial visit and encouraged patients to read the leaflets and try various tools before the next visit.</p> <p>Third, investigators provided a 7-hour joint training session for intervention teams using multiple methods (i.e., lecture, discussion, demonstration, role play with tools). Technicians were trained to assist pharmacists in setting up their blood pressure station, measuring blood pressure values, administering BMQs and other self-report tools, confirming appointments, and rescheduling no-shows (without clerical assistance). Pharmacists were trained to identify and address the targeted barriers to medication adherence and blood pressure control using BMQs and other tools.</p> <p>Fourth, the participating corporations were contracted by the study director to implement the 6-month intervention at TEAM sites. Intervention teams received release time for training and generally scheduled one 2-hour blood pressure clinic per week during hours of overlapping staff, allowing them to focus</p>	<p>Environmental context and resources</p> <p>Environmental context and resources</p> <p>Behavioural regulation</p> <p>Memory, attention and decision processes</p> <p>Social influences</p> <p>Knowledge</p> <p>Environmental context and resources</p> <p>Reinforcement</p>	<p>Resources</p> <p>Resources</p> <p>Self-monitoring</p> <p>Memory</p> <p>Social support</p> <p>Knowledge</p> <p>Barriers and facilitators</p> <p>Incentives</p>	<p>Furniture</p> <p>Take home toolkit</p> <p>Wallet card</p> <p>Medication box</p> <p>Two way communication Training session</p> <p>Release time</p> <p>Modest compensation</p>					
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	on study patients. Participating corporations received modest compensation for documented interventions and training; patients received no compensation for keeping TEAM appointments. To address potential barriers to implementation, district managers and supervisors served on a protocol advisory group led by the study director.							
Tinsel 2013	Those GPs who had been allocated to the intervention group took part in an SDM training programme which had been evaluated in various studies. It was adapted to the requirements of antihypertensive treatment in general practice and entailed six hours in total. The training included the following elements: (1) information on arterial hypertension, (2) physician-patient communication and risk communication, (3) the process steps of SDM, (4) motivational interviewing, (5) introduction of a decision table listing options to lower CVR, and (6) use of case vignettes for role plays simulating physician-patient consultations. Additionally, we recommended implementing a cardiovascular risk calculator for GPs which included elements of SDM. Furthermore we delivered patient information flyers to the GPs of the intervention group. The intervention took place before the T1 data assessment.	Memory, attention and decision processes  Knowledge  Environmental context and resources  Skills  Social influences  Beliefs about consequence  Professional/social role and identity	Attention  Knowledge  Resources  Interpersonal skills  Social support  Outcome expectancies  Professional role	Intervention (focuses attention)  Information  Flyers  Physician-patient communication Shared decision making Decision table  Role plays	GPs of the control group treated their patients as usual.			
Wong 2013	Participants received both usual care followed by community-based medication counselling service immediately after physician consultation. The counseling took place in a consultation room in the same clinic, where the pharmacists counseled the patients resembling their medication adherence intervention in the community. The service is delivered by community pharmacists from a Non-Governmental Organization, including: (1)	Memory, attention and decision processes  Social influences  Knowledge	Attention  Social support  Knowledge	Intervention (focuses attention)  Medication counselling  Reinforcing relevant knowledge	Participants assigned to the usual care group were educated on their diagnoses of hypertension, their implications, and discussed on the importance of proper medication compliance to control hypertension by the attending physicians. Most of these sessions lasted for 2–3 minutes, resembling	Memory, attention and decision processes  Knowledge  Beliefs about consequences	Attention  Knowledge  Outcome expectancies	Intervention (focuses attention)  Educated  Importance of proper medication compliance

	<p>addressing participants' concern and uncertainties in taking medications; (2) reinforcing relevant knowledge on the chronic diseases they are suffering from; (3) education on the proper methods to take their medications, including drug taking dosage, frequency and special precautions if applicable; and (4) provision of medication knives and pill boxes as judged necessary by the pharmacist. Most of the sessions lasted for 15–20 minutes, and all interventions were tailored made to the specific needs of each patient. Participant goals designed to enhance antihypertensive medication adherence referred to the measurement of the Morisky self-reported adherence questionnaire scores. They received comprehensive pamphlets summarizing the content of medication counseling and were motivated to enhance compliance to antihypertensive agents. All participants in this group were offered free-of-charge telephone consultations with community pharmacists within the study period. All community pharmacist interventions were standardized according to content and format. To avoid inter-pharmacist variations, only one pharmacist conducted all interventional sessions at baseline throughout the study.</p>	<p>Beliefs about consequences</p> <p>Environmental context and resources</p> <p>Goals</p> <p>Environmental context and resources</p> <p>Social influences</p>	<p>Outcome expectancies</p> <p>Resources</p> <p>Goal setting</p> <p>Resources</p> <p>Social support</p>	<p>Concerns and comorbidities</p> <p>Medication knives</p> <p>Participant goals Pamphlets</p> <p>Telephone consultations</p>	<p>real clinical practice.</p>			
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## Appendix V. Characteristics of included studies

Amado (2011)	
Methods	Randomized controlled trial
Participants	<p>The study location was Primary Health Care Centres (PHCC), Barcelona and its metropolitan area, Spain</p> <p>515 participants were randomized to the intervention group and 481 participants were randomized to the control group</p> <p>The inclusion criteria were patients between 18 and 80 years old with hypertension who were visiting the clinic for at least 6 months for long-term follow-up and control of hypertension using anti-hypertensive drug therapy</p> <p>The exclusion criteria were serious psychiatric, physical, or sensory alterations</p>
Intervention	<p>Intervention: INTERVENTION (IG)</p> <p>Patients in the Intervention Group (IG) had 4 visits with specially trained nurses who used standardized guidelines and who had attended a 10-hour workshop that focused on the antihypertensive medications. Each visit lasted for an average of 15 minutes.</p> <p>Information was personalized to the needs of the patient. Schedule sheets with the treatment plan were provided, which contained information on the prescribed drugs and dosage schedule as well as basic advice on how to maximize the treatment schedule. The sheets were provided to reinforce the nurse's verbal instructions</p> <p>Control: CONTROL GROUP (CG)</p> <p>Control patients received usual clinic care without any standardized intervention</p>
Outcomes	<p>Adherence measures: Self report - Haynes- Sackett and Morisky-Green tests. Pill count.</p> <p>Patient outcome: systolic and diastolic blood pressure, hypertension control, BMI, and number of hypertensive drugs at 12 months compared with baseline measures</p>
Notes	

Baird (1984)	
Methods	Random allocation without indication of concealment.
Participants	<p>The study location was Canada.</p> <p>193 patients were randomised to the intervention group and 196 to control.</p> <p>Mild-moderate hypertensive patients who, at the time of study entry, were adequately controlled with a regimen of metoprolol 200 mg (range 150 to 250 mg) daily, or propranolol 160 mg (range 120 to 200 mg) daily, either as monotherapy or in conjunction with a diuretic were included in the study. Patients excluded from the study were those with a condition in which beta-blockade was contraindicated</p>
Intervention	Patients were taken off whatever beta-blocker they were taking at entry and then allocated to one of the 2 interventional groups: (1) Betaloc tablets 100 mg in the morning (0600 to 0900 hours), and in the evening (12 hours later), or (2) Betaloc Durules 200 mg every morning (0600 to 0900 hours)
Outcomes	<p>Adherence measures: pill count at 6 and 10 weeks. Spot checks of metoprolol concentration in the urine at 6 and 10 weeks.</p> <p>Patient outcomes: The mean heart rate, systolic and diastolic blood pressures were assessed before, during, and after the trial, and compared between the 2 treatment regimens</p>
Notes	Outcome assessments were not blinded to study group

Becker (1986)	
Methods	Random allocation without an indication of concealment
Participants	<p>The study location was Temple University School of Medicine, Pennsylvania, USA.</p> <p>86 randomised to intervention and 85 to control group.</p> <p>Patients between the ages of 20 and 80 years who were already taking medication for previously diagnosed hypertension, and who had already demonstrated poor blood pressure control (diastolic blood pressure &gt; 90 mm Hg) on at least 1 visit during the preceding 2 years were included in the study. Patients who had significant visual, auditory, or mental problems that could interfere with their adherence were excluded</p>
Intervention	<p>Intervention: PACKAGING INTERVENTION:</p> <p>Patients assigned to the experimental group received all their medications in the special packaging format (all pills taken</p>

	<p>together were packaged in a single plastic blister sealed with a foil backing on which was printed the day of the week and the time of day at which each medication was to be taken).</p> <p>Control: USUAL CARE</p> <p>Patients in the control group received all of their antihypertensive medications in the traditional pill vials (separate vials for each pill that were labeled with the drug name, the dosage, the medication instructions, and the physician's name),</p> <p>All medications for both groups were provided free of charge to ensure that all patients would receive their medications</p>
Outcomes	<p>Adherence measures: Self report - Patients were asked non threatening, non-judgmental questions about their adherence behaviour (patients who admitted less than perfect adherence were considered non-adherent), pill counts (patients were considered adherent if they had taken 80% or more of their prescribed medication) and the Hybrid model were employed in order to assess adherence.</p> <p>Patient outcome: Blood pressure was taken 3 times during each visit. The first measure was discarded and an average of the second and third measures was used as the blood pressure measurement for that visit. Blood pressure control was defined as diastolic blood pressure less than 90 mm Hg</p>
Notes	<p>All data collection was done by a nurse research assistant prior to regular office visits. Physicians caring for patients were aware that adherence studies were in progress, but were not told the aims of the study nor the group to which an individual patient had been assigned</p>

Dusing (2009)	
Methods	Randomized controlled trial
Participants	<p>The study location was not provided.</p> <p>101 participants were randomized to the intervention group and 105 participants were randomized to the control group.</p> <p>The inclusion criteria were patients at least 18 years of age who were either newly diagnosed or not treated for at least 1 year. Except for hypertension, patients had to be healthy and not requiring any regular long-term drug treatment (e.g. for asthma, chronic obstructive pulmonary disease (COPD), diabetes, rheumatoid arthritis, pain medication, depression, psychotropic drugs, inflammatory bowel disease, estrogen replacement therapy, thyroid hormones, hypercholesterolemia, and oral contraception)</p>
Intervention	<p>Intervention: MULTIFACTORIAL INTERVENTION The set of supportive measures provided for selected centers and all patients recruited in these centers is listed below. It was up to the patients to select the tools they would like to use on an individual basis. For</p>

	<p>the patient: (a) 24-hour timer: the timer can be set to an individual time and provides an acoustic signal every 24 hours at this point of time; (b) Set of 10 reminding stickers to be positioned at prominent places at home (e.g. refrigerator and bathroom mirror); (c) Information brochure for patients with hypertension published by the German Hypertension Society; (d) Information letter for the patient; (e) Information letter the patient can give to next of kin to receive support or his therapy (e.g. spouse reminding of drug intake); (f ) Home BP measurement device; (g) Booklet to document home BP measurements</p> <p>Control: STANDARD CARE At the baseline visit, all eligible patients were started on study treatment with valsartan 160 mg daily for 4 weeks. Patients with controlled BP were continued on treatment with valsartan 160 mg. Patients not achieving BP values less than 140/90 mm Hg by week 4 were then uptitrated to valsartan 160 mg and hydrochlorothiazide (HCTZ) 12.5 mg as a fixed-dose combination. Follow-up visits were scheduled after 2 (3rd visit) , 4 (4th visit), 8 (5th visit), 14 (6th visit), 24 weeks (7th visit), and at the end of the observation period at 34 weeks (8th visit). Dispensing of the study drugs was as follows. At baseline, patients received MEMS bottles containing 48 tablets of 160 mg valsartan. At 4th and 5th visits, that is, after 4 and 8 weeks, patients received further MEMS bottles containing 48 tablets of either 160 mg valsartan or 160 mg valsartan and 12.5 mg of HCTZ depending on their BP. At the 6th and 7th visits, that is, after 14 and 24 weeks of treatment, patients received MEMS bottles containing 76 tablets. Patients were instructed to take their medication per mouth with water in the morning between 0700 and 1100 hours, regardless of meals. No supportive measures were given to patients</p>
Outcomes	<p>Adherence measures: electronic MEMS, which compiled date and time of drug intake through the opening of the medication bottle for every day. The MEMS monitors were drug containers designed to compile the dosing history of ambulatory patients prescribed oral medications. Each monitor consisted of a conventional medicine bottle filled with a special closure that recorded the time and date of each opening and closing of the container through integrated microcircuitry. Monitors were designed to be used by one patient with one drug. A communicator transferred the dose-timing data from the MEMS monitor to a computer. At the 2nd and 6th visits, MEMS monitors were to be provided for all patients. At the 6th and 8th visits, the monitors used by the patients were collected by the investigator for data analysis</p> <p>Patient outcomes: blood pressure response and normalization in the 2 randomized groups</p>
Notes	

Friedberg (2014)	
Methods	Randomised controlled trial
Participants	<p>The study location was New York, USA.</p> <p>176 patient were randomised to SMI, 180 to HEI and 177 to control.</p> <p>Patients were eligible if they had hypertension, 2 antihypertensive drug therapy for = 6 months, and uncontrolled BP during screening. Uncontrolled BP was defined as SBP = 130 mm Hg or diastolic BP = 80 mm Hg in diabetes mellitus (DM) or chronic kidney disease, or SBP = 140 mm Hg or diastolic BP = 90 mm Hg in all others as per the BP guidelines at the time of the study . Patients with cardiovascular disease diagnosed &lt;6 months ago, class III or IV heart failure, severe psychiatric illness, AIDS, tuberculosis, lupus, end-stage renal failure, or limited life expectancy (&lt;1 year) were excluded because of terminal illnesses. Other exclusions included lack of a telephone, inability to follow the study protocol, recent major surgery (&lt;3 months), those temporarily in the area or not available for follow-up, or inability to provide informed consent.</p>
Intervention	<p>Intervention: STAGE MATCHED INTERVENTION</p> <p>Patients in SMI received tailored monthly phone counseling for exercise, diet, and medications based on the current stage of change, using a computer-based intervention manual. During each call (~30 minutes), the stage of change for adherence to diet, medication, and exercise was assessed separately using the validated stage of change questions and tailored counseling based on this assessment. The stages of change were precontemplation or no plans to adhere in &lt;6 months; contemplation or plans to adhere in 1 to 6 months; preparation or plans to adhere within 1 month; action or adherence for &lt;6 months; and maintenance or adherence for =6 months. Patients were considered adherent to diet if they reported eating the appropriate diet for hypertension (low in salt and fat with fruits, vegetables, and low-or nonfat dairy products) =6 days/wk. Specific recommendations, such as trimming visible fat from meat and asking for sauces on the side in restaurants were provided each month, and any additional dietary questions were answered. The intervention was tailored to target personal barriers and brainstorm solutions. Medication adherence was defined as the self-report of taking BP medications as prescribed for =6 days/wk. Although refill compliance was measured, the stage of change only took self-reported adherence into account. Exercise adherence was defined as self-reported aerobic exercise for =3 days/wk for =20 minutes each time. We used the lower threshold for exercise adherence because of our patient population with multiple comorbidities, consistent with Federal guidelines for older adults with chronic conditions.<sup>21</sup> Patients received tailored counseling for</p>

	<p>each target behavior based on their current stage of change. SMI used the processes of change using the cognitive and behavioral activities found to be most effective for each stage and incorporated decisional balance and self-efficacy. For the decisional balance, the pros and cons of each behavior were elicited, and the counselor explored why each pro endorsed was important to the participant. For each con, alternatives were explored using problem solving methods. Similarly, for self-efficacy, the counselor worked with the participant to enhance confidence in ability to adhere.</p> <p><b>Intervention: HEALTH EDUCATION INTERVENTION</b>  Patients in (HEI) had monthly telephone counseling (~15 minutes) of standard, nontailored information about hypertension, and diet, medication, and exercise guidelines for hypertension from American Heart Association educational materials. Although HEI did not take the stage of change into account, it was still interactive in encouraging the participants to ask questions. Because the HEI is shorter than the SMI, we included education on other healthful behaviors (expanded hypertension information; sun safety; flu prevention; sleep hygiene; back injury prevention; and vision and hearing) to increase the duration of attention provided.</p> <p><b>Control: USUAL CARE</b>  The control condition was usual care. All participants received standard information about hypertension and its treatment at enrollment. The UC group received no counseling.</p>
Outcomes	<p>Adherence measure: self-report Morisky Medication Adherence Scale measured at baseline and 1 and 6 month follow up.</p> <p>Patients outcomes: BP control at 6 months - A research assistant measured BP 6× for 2 hours using an Omron HEM-907XL automated BP machine at baseline and follow-up time points. By RA in the clinic at baseline and 6 months  SBP - A research assistant measured BP 6× for 2 hours using an Omron HEM-907XL automated BP machine. By RAs in the clinic at baseline and 6 months</p>

Friedman (1996)	
Methods	Random allocation using a paired randomization protocol
Participants	<p>The study location was Boston, USA.</p> <p>133 patients were randomised to intervention and 134 to control.</p> <p>Patients were 60 years or older, under the care of a physician for hypertension, and prescribed an antihypertensive medication. They needed to have systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 90 mm Hg based on an average of 2 determinations taken 5 minutes apart.</p>

	Individuals were excluded if they had a life-threatening illness, were not English-speaking, did not have a telephone or could not use one, or refused to consent to participate
Intervention	<p>Intervention: TELEPHONE LINKED COMPUTER SYSTEM The intervention group received regular medical care plus the telephone-linked computer system (TLC). TLC is an interactive computer-based telecommunications system that converses with patients in their homes, using computer-controlled speech, between office visits to their physicians. The intervention patients would call the TLC on a weekly basis. Before calling, subjects would record their own blood pressure using an automated sphygmomanometer with a digital readout. During the conversation, subjects would answer a standard series of questions and the TLC would provide education and motivational counseling to improve medication adherence. The TLC then transmitted the reported information to the subject's physician</p> <p>Control: USUAL CARE Control participants received usual care.</p>
Outcomes	Antihypertensive medication adherence was assessed by home pill count conducted by the field technicians Clinical outcome measures included change in systolic and diastolic blood pressure. Outcome measures were recorded by the field technicians, at the 2 home visits performed 6 months apart. The measures were also reported on a weekly basis by the participant
Notes	

Girvin (1999)	
Methods	Randomization was conducted by an independent advisor by resampling without replacement after the placebo run-in period. The study was not double-blind because one outcome was the difference in compliance between once-daily and twice-daily regimens. However, the investigator responsible for analyzing the results was blinded as to the treatment phase
Participants	<p>The study location was Northern Ireland.</p> <p>27 patients with a history of mild hypertension (well controlled on monotherapy), with a diastolic BP between 90 to 110 mm Hg were included. Patients were excluded if they had secondary hypertension or significant end organ damage, were pregnant or lactating mothers, had cardiovascular complications in addition to hypertension (e.g. MI within the past 6 months), stroke, congestive heart failure, angina pectoris, had poor renal function, a history of renal artery stenosis, were obese (weighing over 125% of ideal body weight), had hyperkalemia, had a history of angioneurotic edema, had any contraindication or hypersensitivity to ACE inhibitors, or if they were taking nonsteroidal anti-inflammatory drugs, corticosteroids or any other medication that would significantly alter blood pressure</p>

Intervention	<p>Patients were randomly assigned to a sequence of enalapril 20 mg once daily or 10 mg twice daily in 3 4-week periods following a 4-week run-in period. Treatment A comprised enalapril 20 mg once daily, and treatment B comprised enalapril 10 mg twice daily. The first 2 periods in each group constituted a conventional 2-period cross-over design. The third treatment period was included to detect any carryover effects between the periods without having to incorporate a washout phase between treatments. The 4 study arms were organized as follows (each period lasted 4 weeks): ABB BAA ABA BAB</p>
Outcomes	<p>Adherence measures: pill counts MEMS</p> <p>Patient outcomes: blood pressure reduction was measured at each visit. Patients were asked not to take their blood pressure tablet on the morning of the clinical visit until after the investigator had measured their blood pressure so that the blood pressure (BP) readings were trough values. 2 readings were taken after 10 minutes rest in the seated position. The arm was supported at heart level and the diastolic blood pressure taken as the disappearance of the Korotkoff sounds (phase V). Ambulatory blood pressure was measured at the end of the placebo run-in period and at the end of periods 1 and 2</p>
Notes	

Greer (2014)	
Methods	Randomised controlled trial
Participants	<p>The study location was 2 Baptist churches and 1 community center, Northeast Texas, US.</p> <p>30 participants were randomized to the intervention group and 30 participants were randomized to the control group</p> <p>Inclusion criteria were (a) self-identification as black or AA 18 years or older; (b) diagnosis of primary HTN; (c) a resting SBP greater than 140 mm Hg or a DBP greater than 90 mm Hg; (d) ability to read, understand, and speak English; and (e) prescriptions for 1 or more antihypertensive medications. They excluded women who were pregnant, had a history of stroke or myocardial infarction within the last year, were diagnosed with end-stage renal disease and on dialysis, or were currently participating in another research trial on HTN.</p>
Intervention	<p>Intervention: CULTURALLY TAILORED EDUCATION INTERVENTION</p> <p>The culturally tailored intervention consisted of six 90-minute sessions offered once a week for 6 weeks to groups of 8 to 12 women. The groups were led by the author (DBG) who has a</p>

	<p>background in cardiovascular nursing. The 14 standards derived from the Office of Minority Health Culturally Linguistic Appropriate Standards were used as a framework.<sup>17</sup> Key Culturally Linguistic Appropriate Standards followed included race concordance of the RAs and author (DBG), culturally tailored educational materials that were easy to understand, setting in the AA community, culturally appropriate language respectful of AAs, and an ongoing assessment of the intervention through participant feedback. Terms known to participants were used to discuss pressure medicine, fluid pills, use of pickle juice and other folk remedies to lower high blood, and hidden sources of salt. Participants were given a blank family tree to outline ancestors and descendants, and discussions on medication adherence were tied to ancestors and descendants (and their medical histories). Participants were asked to discuss managing medication adherence, adverse effects, and ways of coping with HTN. Content on physical activity, weight management, stroke prevention, and target organ damage was also included. Each session began with prayer and ended with a unity circle and prayer, in which all persons joined hands while 1 person said a prayer. The gospel song Never Would Have Made It<sup>18</sup> was also played at each session. <i>Journal of Cardiovascular Nursing</i> x July/August 2015 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.</p> <p>Content was delivered through lectures, videos, pictures, and handouts in an easy-to-read format. The average Flesch-Kincaid<sup>19</sup> reading level of the materials was grade level 8.5. Of the 60 participants, 11.6% (n = 7) had less than a high school education. The curriculum included materials from the American Heart Association and the National Heart Lung and Blood Institute. Participants were provided with a notebook of materials from the American Heart Association, the National Heart Lung and Blood Institute, and The Power to End Stroke (PTES) Campaign. The PTES DVD,<sup>20</sup> in which laypersons and key celebrities such as the late Yolanda King discuss HBP and stroke prevention, was also shown to participants. Additional content included scriptures on health and wellness, information for increasing healthcare access and resources, the importance of social support, and attitudes and cultural beliefs about HBP.</p> <p><b>Control: WAITLIST CONTROL</b>  Participants randomized to a wait-list control group received only usual care from their healthcare provider.</p>
<p>Outcomes</p>	<p>Adherence measure: Self report - HBCHBPT  The HBCHBPT scale<sup>16</sup> consists of fourteen 4-point Likert-type items (1 = none of the time, 2 = some of the time, 3 = most of the time, and 4 = all of the time). The HBCHBPT scale includes 3 domains of HTN treatment: salt intake, appointment keeping, and medication taking. Scores range from 14 to 56, with lower scores indicating greater adherence. The HBCHBPT scale has demonstrated adequate internal consistency reliability and</p>

	<p>construct and predictive validity with several independent populations of AA and non-Hispanic whites, with Cronbach's alpha values ranging from .74 to .84.16(p93) Cronbach's alpha for this study sample was .89. The operational definition of adherence/compliance is the total score on the HBCHBPT scale. Measured at baseline, at 3 and 6 weeks, and at 6 months.</p> <p>Patient outcome: BP control The clinical measure was blood pressure control, measured before completion of questionnaires using the Omron digital BP device model HEM-780-N3 Intellisense with an adjustable cuff (9Y17 in) (Omron Healthcare Inc, Bannockburn, IL). The Omron digital BP devices were calibrated and tested by a certified biomedical technician before study initiation and at the end of the study. Measured at baseline, at 3 and 6 weeks, and at 6 months.</p>
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Haynes (1976)	
Methods	Random allocation by 'minimization', a method stated to be impervious to bias
Participants	<p>This was the second phase of a 2 phase study.</p> <p>The study location was Canada.</p> <p>20 male steel workers were randomised to intervention and 18 to control.</p> <p>Male steel company employees with high blood pressure (when sitting quietly on 3 separate days, a standard series of fifth phase diastolic blood-pressure were &gt; 95 mm Hg) who were treated with antihypertensive medications during the first phase of the study were included in the second phase if they were non-adherent with prescribed antihypertensive therapy (pill counts less than 80%), and not at goal blood pressures (fifth phase &lt; 90 mm Hg) in the 6th month of treatment of phase 1</p>
Intervention	<p>Intervention: MULTIFACTORIAL INTERVENTION Patients in the experimental group were all taught the correct method to measure their own blood pressures, were asked to chart their home blood pressures and pill taking, and taught how to tailor pill taking to their daily habits and rituals. These men also visited fortnightly at the work site a high-school graduate with no formal health professional training who reinforced the experimental manoeuvres and rewarded improvements in adherence and blood pressure. Rewards included allowing participants to earn credit, for improvements in adherence and blood pressure that could be applied towards the eventual purchase of the blood pressure apparatus they had been loaned for the trial. C</p> <p>Control: USUAL CARE Control patients received none of these interventions</p>

Outcomes	<p>Adherence measure: Pill count</p> <p>An unobtrusive pill count done in the patient's home by a home visitor was the method of determining medication adherence. Adherence rates are reported as the proportion of pills prescribed for the 12th month of therapy which were removed from their containers and, presumably, swallowed by the patients.</p> <p>Patient outcome: BP</p> <p>In the 12th month of treatment, patients were evaluated for adherence and blood pressure both at home and at the mill by examiners who were 'blind' to their experimental group allocation</p>
Notes	

Hosseininasab (2014)	
Methods	Randomised controlled trial
Participants	<p>The study location was an outpatient cardiovascular clinic, Tehran, Iran.</p> <p>98 participants were randomized to the intervention group and 98 participants were randomized to the control group</p> <p>The following inclusion criteria were used: patients aged &gt;18 years; new cases with a diagnosis of mild to moderate hypertension (stage I: 140/90–159/99mm Hg) or those already on antihypertensive treatment but not controlled according to Joint National Committee 7 (JNC 7) guideline; patients who did not have an electronic device for measuring blood pressure at home. The following exclusion criteria were applied: patients with secondary hypertension, severe cardiovascular comorbidities, contraindication for antihypertensive drugs, or serum creatinine &gt;1.5mg/dl. Patients were withdrawn from the study if adverse drug reactions caused cessation of medication therapy.</p>
Intervention	<p>Intervention: HOME BP MONITORING</p> <p>Patients received a wrist blood pressure measurement device (SHB-200w, P/N 323101356; Samsung C&amp;T, Seoul, Korea). They were instructed how to use the device and document their measurements in a logbook. They were advised to measure their blood pressure once daily at a specific time every day. The logbook was checked at each visit by the investigator and was collected at the final visit for data analysis.</p> <p>Control: USUAL CARE</p> <p>In the control condition, patients received usual care as suggested by the physician.</p>
Outcomes	<p>Adherence measure: pill count</p> <p>Pill counting was the main method to calculate patients' adherence to antihypertensive medications during the study period (the 3 follow-up visits). The investigator asked each patient to bring the leftover medications to the clinic. To reduce pill dumping, the</p>

	<p>investigator tried to convince patients not to hide actual consumption by stating that the physician will not be informed about their performance. The pill counting was carried out in a separate room not exposed to the medical care team. Number of consumed pills was calculated and divided by the number of total prescribed pills for each antihypertensive drug. The adherence rate for each drug was calculated separately at each follow-up visit. An average of the adherence rates to all antihypertensive medications was computed as the final adherence rate at each time point.<sup>18</sup> An arbitrary cutoff threshold of 80% was considered an acceptable adherence rate.</p> <p>Patient outcome: BP</p> <p>The primary outcome of the study was office-based blood pressure, which was measured by a digital upper arm device (BM 16, Item no. 4211125/652.02/9; Beurer, Ulm, Germany). At baseline and each follow-up visit, blood pressure was measured twice with a 10-minute interval in resting position. The mean of the 2 measurements was documented. For the intervention group, the average of self-monitoring figures during the last week before each follow-up visit was documented for analysis.</p>
Notes	

Johnson (1978)	
Methods	Random allocation in a 2 x 2 factorial design. No statement concerning concealment of randomization
Participants	<p>Volunteers from shopping center blood pressure screening in Canada, with follow-up by usual family doctors.</p> <p>35 patients were randomised to intervention 1, 34 to intervention 2, 33 to intervention to 33 and 34 to control group.</p> <p>Men and women aged 35 to 65 who had been receiving antihypertensive medications for at least 1 year, but whose diastolic blood pressure had remained elevated</p>
Intervention	<p>Intervention: SELF RECORDING AND HOME VISIT</p> <p>The interventions consisted of (1) self recording and monthly home visits, (2) self recording only, (3) monthly home visits. Subjects in groups (1) and (2) received a blood pressure kit and instruction in self recording. Patients in the self recording groups were to keep charts of their daily blood pressure readings and were instructed to bring these charts to their physician at each appointment. Subjects in groups (1) and (3) had their blood pressure measured in their homes every 4 weeks, and the results were reported to both the patient and the physician</p> <p>Control: USUAL CARE</p> <p>The control group consisted of (4) neither self recording nor home</p>

	visits.
Outcomes	<p>Adherence measure: interview</p> <p>Pill counts (the percentage of prescribed pills that had been consumed was estimated by comparing pills on hand at a home visit with prescription records of pills dispensed and the regimen prescribed) .</p> <p>Patient outcomes: Changes in mean diastolic blood pressure (mm Hg) were assessed. Since the initial blood pressure bears an important relation to the change in blood pressure over time, the change scores were adjusted for differences in entry values by covariance analysis. Outcome assessors were blinded to study group</p>
Notes	

Ma (2013)	
Methods	Randomised controlled trial
Participants	<p>The two community health centres, Haizhu District of Guangzhou City, China.</p> <p>60 participants were randomized to the intervention group and 60 participants were randomized to the control group</p> <p>Patients were recruited in the study if they met the following inclusion criteria: (1) patients older than 18 years who agreed to take part in the study; (2) patients diagnosed with essential hypertension by a cardiovascular physician; and (3) patients who took at least one antihypertensive medication. The participants were excluded, as follows, if they were: (1) secondary hypertensive patients or (2) pregnant women.</p>
Intervention	<p>Intervention: MOTIVATIONAL INTERVIEWING</p> <p>The counselling intervention was based on MI and social cognitive theory [7,23] and was designed to address hypertension care. It focused on the patients' behaviour changes, such as taking medication on time, healthy dietary habits, regular physical activity, drinking and smoking cessation and reducing stress. An MI-based counselling protocol was established, which included the following steps: (1) build rapport with the patients; (2) evaluate the patients' confidence and motivation for behaviour changes and their self-efficiency; (3) help the patients become aware of and address the ambivalence blocking their behaviour to change; (4) help the patients find the discrepancies between their values and their current behaviours; (5) provide strategies of adherence to behaviour changes; (6) summarise the pros and cons of the proposed behaviour changes; (7) set realistic and specific goals for behaviour modification; (8) prompt the patients to follow the plan for behaviour change; and (9) provide an overall summary of the</p>

	<p>MI session and the patients' performances [9,24]. The nurses asked the patients to record a daily diary, and the content included information on adherence to medication, dietary habits, physical activity, drinking and smoking, illness perception, physical health, and mental health. The nurses assessed the patients' performance according to the recorded diary during interviews with the patients and were aware of the status quo of the patients' medication adherence and lifestyle changes. The next goal would be established based on the diary. MI was conducted by the trained nurses. Each nurse was responsible for five patients. MI was performed at the patients' homes or the community health centres by appointment between the nurses and patients. The duration of the MI was approximately 30–40 min for each session. The patients received MI eight times over six months.</p> <p>Control group: USUAL CARE The patients in the control group accepted the usual care, which consisted of the provision of hypertension information and recommendations to improve treatment adherence and change unhealthy lifestyles. The cardiologists or specialist nurses delivered a lecture on hypertension prevention for these patients every 6 weeks. The leaflets concerning hypertension information were freely delivered to the patients.</p>
Outcomes	<p>Adherence measure: Self-report The adherence measure was self-reported using the medication adherence subscale of the Treatment Adherence Questionnaire of Patients with Hypertension (TAQPH) at baseline and follow-up.</p> <p>Patient outcome: BP The clinical outcome was blood pressure. Nurses at the two community health centres took the BP of the patients during their outpatient visits in the two different phases of the study without joining the study. They used an identical type of calibrated digital BP monitor (Model FT-A11-2, Fudakang Industry Co., Ltd., Shenzhen, China) to measure the BP of each patient. The BP was measured in a seated position using an appropriately sized cuff after an initial rest period of 10 minutes. The nurses who conducted the MI or usual care collected the laboratory values from the patient medical records after the patients completed the first and second questionnaires.</p>
Notes	

Margolius (2012)	
Methods	Randomized controlled trial
Participants	The study location was the Family Health Center in San Francisco General Hospital, San Francisco, USA.

	<p>129 participants were randomized to the intervention group and 108 participants were randomized to the control group.</p> <p>The inclusion criteria were patients with blood pressures of at least 145 systolic or at least 90 diastolic mmHg, measured by the medical assistant at the enrollment visit and at least 1 previous visit in the last 12 months (based on chart review) The exclusion criteria were an age of younger than 30 years; not speaking English, Spanish, Cantonese, or Vietnamese; a creatinine level of greater than 1.5 mg/dl; New YorkHeart Association class III or IV heart failure; a life expectancy of less than 1 year; or being identified by one's primary care clinician as unable to follow instructions because of physical or cognitive disability, psychiatric illness, or other reasons</p>
Intervention	<p>Intervention: HOME TITRATION GROUP Clinicians of patients in the home-titration arm completed an algorithm of antihypertensive medication adjustments. Health coaches made weekly telephone calls to participants in both study arms to discuss overall well-being, adherence to action plans, and blood pressure values. Patients in the home-titration arm who reported blood pressure greater than 140 mmHg systolic or greater than 90 mmHg diastolic and excellent medication adherence could choose to increase their antihypertensive medication regimen according to the algorithm without a clinician appointment. In those cases, health coaches notified a physician investigator to fax the prescription to the pharmacy. Clinicians were notified of medication changes by e-mail, and health coaches entered the change in the electronic health record. The duration of the intervention was 6 months</p> <p>Control: NO HOME TITRATION Home monitoring and health coaching alone (no home-titration arm), included health coaches made weekly telephone calls to participants in both study arms to discuss overall well-being, adherence to action plans, and blood pressure values. The duration of the intervention was 6 months</p>
Outcomes	<p>Adherence measure: Self-report Health coaches recorded the number of days in the past week patient reported having missed taking a blood pressure medication. 6 months after study completion, patients' electronic health records were reviewed for the number of blood pressure medications at enrollment and at 6 months</p> <p>Patient outcomes: BP Systolic blood pressure was the primary outcome. Blood pressure was measured at baseline and 6 months. Patients were asked to come to the clinic, and blood pressure was measured by the medical assistant using the standard procedures: patients were seated at the nurse station for at least 5 minutes before blood pressures were measured with an automated machine on 1 arm.</p>

	No of clinic visits Electronic records were used to obtain information about the number of primary care visits made by each patient in the 6 month before, during and after the study
Notes	

Marquez Contreras (2005)	
Methods	Randomised controlled trial.
Participants	<p>The study location was Spain.</p> <p>Patients (n = 636) were randomly allocated to receive 1 of the 2 interventions, the telephone intervention (n = 216) or the mail intervention (n = 212), or usual care (n = 212).</p> <p>Patients were eligible for participation in the trial if the following criteria were met: (i) Outpatients of either sex and between 18 and 80 years of age; (ii) newly diagnosed or uncontrolled phase I and II hypertension (JNC-VI criteria) requiring antihypertensive treatment; (iii) provision of patient informed consent in writing</p> <p>Patients were excluded if they met any of the following criteria: (i) Patients who at the start of the study required 2 or more antihypertensive drugs for hypertension control; (ii) acute myocardial infarction; (iii) secondary hypertension; (iv) known side effects and contraindications to the use of angiotensin AT1 inhibitors; (v) pregnant or breastfeeding women; (vi) patients with conditions capable of interfering with the study; (vii) patients planning to donate blood; (viii) participants in other research studies; (ix) patients cohabiting with another person taking the same antihypertensive medication</p> <p>Study withdrawal criteria were as follows: (i) Inadequate therapeutic effect requiring an increase of more than 20% in the scheduled number of visits; (ii) patient decision not to continue with the study and/or schedule follow-up visits; (iii) concomitant illnesses or adverse effects that in investigator opinion, the patient needs be withdrawn from the study</p>
Intervention	<p>Intervention: TELEPHONE INTERVENTION GROUP</p> <p>Participants allocated to the telephone intervention group (TIG) received a controlled intervention in the form of 3 telephone calls: the first 15 days after the inclusion visit; the second and third being one week after visits 3 and 4. The telephone intervention was made by 2 expert nurses in this type of interventions. During the calls to patients in this group, the patients were reminded of scheduled visits and asked about the name, dosage, and timing of their antihypertensive medication, and the number of remaining tablets. Patients were informed, according to the number of tablets in their possession, if they had good or poor compliance. In the event of good compliance, the patients were congratulated and encouraged to continue adhering to therapy. In the event of noncompliance, the patients were encouraged to comply, and the associated benefits</p>

	<p>were explained.</p> <p><b>MAIL INTERVENTION GROUP</b></p> <p>For participants who were allocated to the mail intervention group (MIG), they received 3 mailed communications at home: the first 15 days after the inclusion visits; the second and third, being one week after visits 3 and 4; in order to promote compliance through health education in hypertension, reinforce compliance, and remind the subjects of the scheduled visits. The mailed messages included information about the following hypertension aspects: what is hypertension?; diagnosis of hypertension; symptoms; related risk factors; why is necessary to treat the hypertension?; what is the hypertension treatment?; and information about the correct taking of medication.</p> <p><b>Control: USUAL CARE</b></p> <p>Patients who were allocated to the control group (CG) received the center's routine primary care intervention and did not receive any additional intervention to improve adherence</p>
Outcomes	<p><b>Adherence measure: Pill count</b></p> <p>Percentage compliance (PC) was calculated from the following formula: <math>PC = (\text{total no. of presumably consumed tablets} / \text{total no. that should have been consumed}) * 100</math>. Compliance was accepted if it was in the range of 80% to 110%. The study final PC for each patient was defined as the cumulative PC at the end of follow-up (at the end of the last visit or at the time of withdrawal), while the monthly PC was taken to be the PC recorded between one follow-up visit and the next.</p> <p><b>Patient outcome: BP</b></p> <p>Blood pressure was measured as the clinical endpoint during the scheduled visits by the primary care physician. The final blood pressure reading was taken as the mean of the 2 measurements made</p>

Marquez Contreras (2006)	
Methods	Randomised controlled trial
Participants	<p>The study location was Spain.</p> <p>100 patients were randomised to intervention and 100 to control</p> <p>Patients were ambulatory patients between 18 and 80 years of age, newly diagnosed hypertensive patients or those already on antihypertensive treatment but not controlled and who did not have an electronic monitor for home blood pressure measurement (HBPM), patients with phase I or II arterial hypertension (AHT) according to the JNCVI criteria, and patients who had given their</p>

	written consent. Patients were excluded from the study if they were requiring 2 or more antihypertensive drugs at the start of the study, secondary AHT, pregnant or breast-feeding women, patients with diseases that could interfere with the study, patients who intended to donate blood, patients who were unable to give their consent, patients participating in other studies, and patients co-habiting with other individuals taking the same antihypertensive medication
Intervention	<p><b>Intervention: HOME BP MONITORING</b>  Patients in this intervention, apart from receiving the usual care, also received an OMRON automatic monitor for home blood pressure measurement (HBPM). The patients received a kit in their home containing the monitor, an instruction manual, a summary of the functions, and a card on which to note the measurements. They were advised to follow the HBPM program, which consisted of measuring the BP 3 days a week (Tuesdays, Thursdays, and Saturdays), twice before breakfast (0800 to 1000 hours) and twice before supper (2000 to 2200 hours) and record these results on the card (4 times a day) . The patients received a phone call to explain how to use the monitor and follow the HBPM program.</p> <p><b>Control: USUAL CARE</b>  The control intervention involved patients receiving the care usually provided by their general practitioners</p>
Outcomes	<p><b>Adherence measure: MEMS</b>  The percentage compliance (PC) was calculated by dividing the total number of tablets the patients were assumed to have taken by the total number of tablets that the patients should have taken and multiplying by 100 to obtain a percentage. Compliance was considered to be present in patients with a percentage compliance between 80% and 100%</p> <p><b>Clinical outcome: BP</b>  Blood pressure (taken as the mean of 2 measurements)</p>
Notes	

Matsumura (2012)	
Methods	Randomized controlled trial
Participants	<p>The study location was 29 hospitals or clinics in Japan.</p> <p>103 participants were randomized to the intervention group and 104 participants were randomized to the control group.</p> <p>The inclusion criteria were 20 years or older, hypertension, who could be treated with angiotensin II receptor blockers (ARBs) and diuretics (thiazides or related sulphonamide compounds) The exclusion criteria were extremely high blood pressure (<math>\geq 200</math> mm Hg in systolic or <math>\geq 120</math> mm Hg in diastolic blood pressure), or a serious renal or liver dysfunction, taking more than 4 tablets excluding the study drugs</p>

Intervention	<p>Intervention: COMBINATION PILL The intervention was a combination pill instead of multiple pills. Patients assigned to the intervention group received a combination pill (losartan 50 mg/hydrochlorothiazide 12.5 mg). Follow-up was done at 1, 3, and 6 months</p> <p>Control: MULTIPLE PILLS Control patients were provided with an angiotensin receptor blocker and a diuretic. Follow-up was done at 1, 3, and 6 months. Adherence outcomes and blood pressure were measured at the 1, 3, and 6-month appointments; patient outcomes at before and 6 months after randomization</p>
Outcomes	<p>Adherence measure: pill counts Adherence rates were calculated for each visit using the following formula: adherence rate (%) = [ (number of prescribed pills - number of residual pills)/number of prescribed pills] × 100. Non-adherence was defined as an adherence rate of less than 90%</p> <p>Patient outcomes: BP After resting for at least 5 minutes, blood pressures were measured twice in a sitting position using a standard sphygmomanometer. The mean of 2 measurements was used in the present analysis.</p> <p>Blood variables Blood variables including hematocrit, serum creatinine, serum sodium, serum potassium and serum uric acid were measured before and 6 months after randomization.</p> <p>Adverse events</p>
Notes	

Morgado (2011)	
Methods	Randomized controlled trial
Participants	<p>The study location was University Hospital of Cova da Beira, Covilha, Portugal.</p> <p>98 participants were randomized to the intervention group and 99 participants were randomized to the control group.</p> <p>The inclusion criteria were all adults of 18 years or more with established diagnosis and under treatment for arterial hypertension regardless of BP control The exclusion criteria were dementia, pregnancy, and breastfeeding</p>
Intervention	Intervention: PHARMACIST INTERVENTION PROGRAM In sessions at baseline (30 minutes) and 3 and 6 months follow-up (20 minutes) the clinical pharmacist thoroughly interviewed the patient to identify problems with medication adherence, provided patient education and counseling, and provided advice to physicians

	<p>regarding pharmaceutical care. Pharmacists could schedule additional visits as needed, and patients were encouraged to bring all empty medication blisters and boxes to visits</p> <p>Control: USUAL CARE Control group patients received usual care through the hospital clinic. Pharmacists were not involved in their care</p>
Outcomes	<p>Adherence measure: self-report A validated 5-item adherence scale, derived from the Morisky 4-item scale, which was measured at baseline and end of study (9 months) by clinical pharmacists (not blinded to study allocation). Low adherence was defined as answering Yes to at least 3 of the 5 questions</p> <p>Patient outcomes: BP control SBP, DBP Proportion of patients achieving blood pressure control according to the JNC 7 guidelines, reduction in systolic blood pressure, and reduction in diastolic blood pressure at 9 months. These outcomes were based on the mean of 2 consecutive measurements, measured by trained nurses blinded to group allocation, according to the published guidelines on proper blood pressure measurement issued by the Portuguese Society of Hipertension using a validated automatic blood pressure measuring devices (OmronM4-I) and appropriate cuffs.</p> <p>Patient knowledge of target BP values and of hypertension Patients were considered knowledgeable of target BP values if they knew both target BP figures (140/90 mm Hg for hypertensive patients without diabetes and CKD and 130/80 mm Hg for hypertensive patients with diabetes or CKD). They were considered knowledgeable of the negative impacts of hypertension to health if they mentioned at least 2 potential major negative consequences of uncontrolled hypertension to health</p>
Notes	

Ogedegbe (2012)	
Methods	Randomized controlled trial
Participants	<p>The study location was a primary care practice within the ambulatory care network of New York Presbyterian Hospital, New York, New York, USA.</p> <p>125 participants were randomized to the intervention group and 131 participants were randomized to the control group.</p> <p>The inclusion criteria were self identification as African American or black, fluency in the English language, a diagnosis of</p>

	<p>hypertension, and the use of at least 1 antihypertensive medication</p> <p>The exclusion criteria were (i) had a diagnosis of cognitive impairment or serious medical condition as determined by their primary care physician, (ii) were unable to provide informed consent, or (iii) refused to participate</p>
Intervention	<p><b>Intervention: POSITIVE AFFECT INTERVENTION</b> Patients in the Positive Education (PE) control group received a culturally tailored educational workbook designed (1) to enhance patients' knowledge about hypertension, (2) to improve self-management behaviours, and (3) to support goal-setting. Patients randomized to the Positive Affect (PA) intervention group were given the same workbook as those in the PE group but with an additional chapter that addresses the benefits of positive moments in overcoming obstacles to medication adherence. Also, these patients received 2 forms of PA during bimonthly telephone calls. First, they were asked to identify small things in their lives that invoke positive feelings in them and were then instructed to incorporate these positive thoughts into their daily routine. The positive thoughts were further reinforced during subsequent bimonthly telephone calls. Second, the patients received unexpected small gifts mailed to them before each telephone call. This strategy was based on the potential of the receipt of unexpected gifts to induce positive feelings. For self-affirmation induction, the patients were asked to remember their core values and proud moments in their lives whenever they encounter situations that make it difficult for them to take their medications</p> <p><b>Control: PATIENT EDUCATION</b> Patient Education (PE) control group received a culturally tailored educational workbook designed (1) to enhance patients' knowledge about hypertension, (2) to improve self-management behaviours, and (3) to support goal-setting. On receipt of the workbook, trained Research Assistants (RAs) reviewed each chapter with the patients and then asked them to sign a behavioural contract that asked them to make a commitment to taking their medications as prescribed. Subsequent to this session, each patient received bimonthly telephone calls, during which the RAs assessed the patient's behavioural contract and confidence to take their medications as prescribed. These assessments served as the basis for reviewing and counselling the patient on perceived barriers to medication adherence. The intervention lasted for 12 months</p>
Outcomes	<p>Adherence measure: Self report questionnaire for baseline adherence measurement</p> <p><b>MEMS</b></p> <p>Patients taking more than 1 medication could select the medication they wanted to put in the monitor. Monitors were returned to research assistants to have data downloaded or were sent in for downloading at 12 months. Electronic pill monitors are the accepted gold standard for adherence assessment</p>

	<p>Patient outcome: BP change</p> <p>The patient outcomes were change in blood pressure (BP) from baseline to 12 months. BP data were extracted from patients' electronic medical records log of office BP readings taken by nurses or certified medical assistants using standard mercury sphygmomanometers. Blood pressure control was defined as a BP greater than 130/80 mmHg for patients with diabetes or chronic kidney disease and a BP less than 140/90 mm Hg for all other patients</p>
Notes	

Ogedegbe (2015)	
Methods	Randomised controlled trial
Participants	<p>The study setting was low-resource community health centres (CHCs) in New York City, NY, USA.</p> <p>529 participants were randomized to the intervention group and 510 participants were randomized to the control group</p> <p>From the study: Eligibility criteria included patients who self-identified as black or African American, received care at the CHC for = 6 months, had uncontrolled HTN, and were fluent in English.</p> <p>From the protocol: To be eligible, patients must be self-identified as black or African American; be at least 18 years old; be receiving care at the participating CHC for a period of at least six months; have a diagnosis of HTN and uncontrolled BP at the last office visit (BP &gt;140/90); be taking at least one antihypertensive medication. In addition, all patients must have had uncontrolled BP (SBP =140 mmHg OR DBP =90 mmHg) at the time of the consent visit, as measured by BPTru (VSM Medtech, Coquitlam, BC, Canada, Model BPM-300), an automated oscillometric validated BP monitor. Patients are excluded if they are non-English speaking; have an arm circumference of &gt; 42 cm; participate in other hypertension-related trial; currently use home BP monitoring; have cognitive impairment with Mini Mental Status Examination (MMSE) score &lt;24 for patients with &gt; 8th grade education; or MMSE &lt;17 for those with an = eighth grade education; are unwilling or unable to complete screening and/or baseline assessments; or unwilling/unable to provide informed consent.</p>
Intervention	<p>Intervention: CASE ROUNDS</p> <p>Hypertension case conferences and expert consultation involves a strategy of combining CME with academic detailing and peer-to-peer collaborative management. It uses case rounds format to provide real-time specialty consultation on hypertension</p>

	<p>management. These sessions occur monthly for 12 months. Each CHC has the opportunity to present a single clinical case using a standardized format. The hypertension specialists (GO, JR, and TP) provide feedback on the adequacy of current treatment strategies based on JNC-7 recommendations. The case presentations are followed by an open discussion among the participating physicians and the hypertension specialist who delivers the lecture.</p> <p><b>HYPERTENSION KNOWLEDGE:</b> two live one-hour lectures presented at the beginning of the study at each intervention site. These lectures address the major highlights of JNC-7 guidelines with particular emphasis on their relevance to African Americans. The format is a standard 45-minute lecture followed by a 15-minute Question and Answer session (see Webcast Library at <a href="http://www.CDNetwork.org">www.CDNetwork.org</a>).</p> <p><b>PATIENT COUNSELLING</b> Individual and group behavioural counselling sessions on the adoption of lifestyle modifications conducted by trained study staff, CHC dieticians and health educators. Patients receive six group behavioural counselling sessions (monthly) on adoption of recommended lifestyle modifications conducted by trained CHC staff and/or study staff. The specific behaviour change strategies adopted at these sessions include motivational interviewing, goal setting, problem solving, stimulus control, cognitive strategies, and self-monitoring. The target behaviour goals set in collaboration with the patients include dietary changes, weight loss, reduction of sodium intake, increased physical activity, moderation of alcohol intake and adherence to prescribed BP medications. The behavioural counselling sessions are delivered by study and clinical staff at the CHCs, including nutritionists, nurses and health educators, who are all trained by the project director (SF). The training addresses motivational interviewing counselling strategies for improving nutrition, physical activity, weight loss, and promoting medication adherence.</p> <p><b>Control: USUAL CARE</b> Patients at the UC sites receive print versions of the NHLBI publications “Your Guide to Lowering Blood Pressure”; “Facts about the DASH Eating Plan”; and four educational group sessions on the benefits of mineral and vitamin supplementations. Physicians are given the print version of JNC-7 guidelines and a laminated reference card of the JNC-7 treatment algorithm. The physicians also receive CME-accredited webcasts on topics unrelated to HTN, such as asthma, and vitamin supplements.</p>
<p><b>Outcomes</b></p>	<p>Adherence measure: Self-report Morisky Medication Adherence Scale. It was measured at baseline, 6 months, 12 months.</p> <p>Patient outcome: BP control</p>

	The primary outcome was the proportion of patients with adequate BP control (BP<140/90 for all patients or BP<130/80 for those with comorbid diabetes or kidney disease) at 12 months; and the maintenance of intervention effects one year after the trial. The secondary outcomes were within-patient change in BP from baseline to 12 months.
Notes	

Rudd (2004)	
Methods	Randomised controlled trial
Participants	<p>The study location was California, USA.</p> <p>Eligible patients underwent randomization using computer-generated assignment to receive either usual medical care only (UC; n = 76) or usual care plus nurse care management intervention (INT; n = 74).</p> <p>Patients had an elevation of BP to levels greater than 150 mmHg systolic, 95 mmHg diastolic, or both. This was confirmed by the mean of 2 BP values being greater than 150/95 mmHg on 2 screening visits conducted on separate days at least 1 week apart</p>
Intervention	<p><b>Intervention: NURSE CARE MANAGEMENT</b></p> <p>The intervention consisted of the nurse care manager conducting baseline counseling on the correct use of the automated BP device, regular return of the automatically printed BP reports, tips for enhancing drug adherence, and recognition of potential drug side effects. The nurse initiated follow-up phone contacts at 1 week and at 1, 2, and 4 months that averaged 10 minutes in duration. During the phone calls, the nurse asked the patients about each medication dosage and any problems experienced since the previous contact. Patients were encouraged to telephone anytime during regular hours with questions or concerns. The nurse care manager contacted physicians to obtain permission to initiate any new BP drug but did not contact physicians regarding changes in medication dosage.</p> <p><b>Control: USUAL CARE</b></p> <p>Usual care in both groups consisted of patients continuing to receive the routine care that they had received before the study</p>
Outcomes	<p>Adherence measure: MEMS data downloaded using the electronic drug event monitors (eDEMs).</p> <p><b>Patient outcomes: BP</b></p> <p>The same semi-automated portable device was used to measure BP at home and during each clinic visits. At home, patients recorded BP twice daily at the same times each day and each week; the device generated a printed report of up to 14 measurements</p>
Notes	

Sackett (1975)	
Methods	Random allocation, 2 x 2 factorial design, no indication of concealment
Participants	<p>The study location was Canada.</p> <p>114 male steel workers were randomised to intervention and 116 to control.</p> <p>Male steel company employees who exhibited persistently elevated diastolic blood pressure on repeated examination (at or above 95mmHg (5th phase)), were free of secondary forms of hypertension, were taking no daily medication, and had not been prescribed antihypertensive medications for at least 6 months before the trial were eligible for the study</p>
Intervention	<p>Intervention: AUGMENTED CONVENIENCE Subjects in augmented convenience saw company physicians, rather than their family physicians, for hypertensive and follow-up care during paid working hours.</p> <p>MASTERY LEARNING The second intervention was designed to give the facts about hypertension, its effects upon target organs, health, and life expectancy, the benefits of antihypertensive therapy, the need for adherence with medications and some simple reminders for taking pills (this information was provided in a slide-tape format, and reinforced by a secondary school graduate 'patient educator')</p> <p>Control: USUAL CARE Patients in the control condition did not receive augmented convenience or mastery learning.</p>
Outcomes	<p>Adherence measure: pill count Adherence was calculated by comparing the number of tablets prescribed with medications still on hand. Adherence is reported in terms of the per cent of medication prescribed for the 6th month which was removed from the bottle and, presumably, consumed by the patient. Patients whose pill counts were consistent with adherence levels of 80% or more were considered 'compliant'.</p> <p>Urine assay The semi-quantitative identification of drugs and metabolites in the urine, by the identification of characteristic changes in serum potassium and uric acid in men on thiazide drugs.</p> <p>Patient outcome: Blood pressure control Assessed by trained observers. Only patients whose diastolic blood pressure was below 90 mm Hg at 6 months would be designated as being 'at goal blood pressure'. Outcome assessors were blinded to study group</p>

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Schroeder (2005)	
Methods	Randomised controlled trial
Participants	<p>The study location was Bristol, UK.</p> <p>128 patients were randomised to intervention and 117 to control.</p> <p>Patients had hypertension and a latest blood pressure recording of <math>&gt;</math> or <math>=</math> to 150 mm Hg systolic and/or 90 mm Hg diastolic in the past 6 months. Patients were excluded from the study if they did not control their medication intake (such as some nursing home patients), had secondary hypertension, severe dementia or other reasons for not approaching them, such as recent bereavement</p>
Intervention	<p><b>Intervention: NURSE LED ADHERENCE SUPPORT</b>  Patients in the intervention group received, in addition to usual care, a nurse-led adherence support session lasting a maximum of 20 minutes, followed by a shorter reinforcement session (10 minutes) 2 months later. The intervention was aimed to provide an opportunity for patients to talk about any problems with their blood pressure-lowering medication. Practice nurses investigated whether patients understood their diagnosis and agreed with the treatment process. They also addressed patient concerns with their medication and to agree to tailored strategies to resolve any medication problems.</p> <p><b>Control: USUAL CARE</b>  The control group received standard care delivered at their respective practices, apart from blood pressure checks at similar intervals as the participants in the intervention group. Wherever possible, these checks were carried out by another practice nurse who was not involved in delivering the intervention but all practice nurses were made aware of the risk of contamination and encouraged not to change their 'usual practice' for the control patients</p>
Outcomes	<p><b>Adherence measure: MEMS</b>  The primary adherence outcome was measured by Medication Event Monitoring System (MEMS) in the 6 months period following the intervention. Adherence was defined as 'timing compliance', which is the number of doses taken at <math>24 \pm 6</math>-hour intervals for a once daily regimen or <math>12 \pm 3</math> hours for twice daily doses, divided by the total number of days and multiplied by 100%. 2 additional measures of adherence were taken: 1) 'correct dosing', which was the percentage of days on which the correct number of doses was taken; and 2) 'taking compliance', was defined as the percentage of prescribed number of doses taken, equivalent to a 'pill count'.</p>

	<p>Patient outcome: BP</p> <p>Systolic and diastolic blood pressure was measured at baseline as well as 1, 2, and 6 months after randomization</p>
Notes	

Stewart (2014)	
Methods	Randomised controlled trials
Participants	<p>The study locations were pharmacies from metropolitan, regional and remote areas in three Australian states (Victoria, Western Australia and Tasmania).</p> <p>241 participants were randomized to the intervention group and 216 participants were randomized to the control group</p> <p>Inclusion criteria included: Using, or having used in the previous 6 months, at least one antihypertensive medication belonging to the four common classes of antihypertensives in Australia 12 – angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, calcium channel blockers and beta-blockers – or fixed combinations of these antihypertensive medications with other antihypertensives (e.g. diuretics); A diagnosis of primary hypertension confirmed by patient-nominated general practitioner (GP); Aged 18 years or above; and Available for follow-up for at least 6 months from baseline. Exclusion criteria; Participation in other adherence promotion programs; Having had a pharmacist-conducted medicine review in the previous 12 months; Unable to communicate in English; and Not self-administering antihypertensive medicines.</p>
Intervention	<p><b>Intervention: PHARMACY BASED INTERVENTION</b></p> <p>Participants met with pharmacists at baseline, 3 and 6 months to discuss adherence. They also received a package of interventions at baseline including: home BP monitor, training on self monitoring of BP, motivational interviewing and education from the pharmacist, home medicines review, dose administration aid and/or patient medication profile where necessary, medication use review, referral to a GP when needed and refill reminders.</p> <p><b>Control: USUAL CARE</b></p> <p>Participants in the control group received usual care</p>
Outcomes	<p>Adherence measure: Self-report</p> <p>Morisky scale</p> <p>Tool for Adherence Behaviour Screening (TABS).</p>

	<p>Patient outcome: BP control</p> <p>Blood pressure was measured using a home BP monitor (Omron HEM-790IT) with the capacity to store and download BP readings to be used for discussion at three- and 6-month follow-ups.</p> <p>Measured by pharmacist at baseline, 3 months and 6 months</p> <p>Measured by patients at home using home BP monitor (no times/amounts reported).</p>
Notes	

Svarstad (2013)	
Methods	Randomised controlled trial
Participants	<p>The study locations were 28 chain pharmacies, Wisconsin, USA.</p> <p>276 participants were randomized to the intervention group and 300 participants were randomized to the control group</p> <p>Patients had to be 18 years or older and self-identified as black, have one or more blood pressure prescriptions, obtain all blood pressure medications from Walgreens or Aurora pharmacies, have a mean blood pressure of 140/90 mm Hg or more, and be able to read and return for six visits. Exclusion criteria included blood pressure greater than 210/115 mm Hg, kidney dialysis, liver disease, organ transplant, serious memory loss, terminal illness, pregnancy, alcohol/substance use problem, heart failure symptoms, arm circumference greater than 16.5 in, physician exclusion, or employment at the pharmacy.</p>
Intervention	<p><b>Intervention: AUGMENTED PHARMACY SERVICES</b></p> <p>The intervention was based largely on the Health Collaboration Model and involved several unique strategies.<sup>9</sup> First, we developed and provided clinical toolkits for pharmacists and technicians. These userfriendly toolkits included modified Brief Medication Questionnaires (BMQs)<sup>26</sup> and other patient self-report tools for easy identification and monthly assessment of the “core” barriers targeted in this trial (patient misunderstandings of blood pressure goals and regimen; patient doubts or concerns about drug efficacy, adverse effects, and long-term effects; and difficulties remembering, paying, or refilling on time). Pharmacy technicians asked patients to complete these self-report tools in the waiting area before they met with pharmacists, saving time for staff and patients. In addition to patient self-report tools, the clinical toolkits included simple algorithms for addressing identified barriers, one-page checklists for documenting and tracking barriers and interventions, structured tools for faxing feedback to physicians (if needed), and validated blood pressure monitors and portable</p>

	<p>furniture for a semiprivate blood pressure station. Second, we developed and provided one take-home toolkit for each patient. This patient toolkit included a wallet card for recording blood pressure readings, 7-day medication box for remembering doses, easy-to-read leaflets for increasing patient awareness and involvement in the TEAM program, and a pedometer for reinforcing lifestyle change. Pharmacists used various tools to facilitate two-way communication during the initial visit and encouraged patients to read the leaflets and try various tools before the next visit. Third, investigators provided a 7-hour joint training session for intervention teams using multiple methods (i.e., lecture, discussion, demonstration, role play with tools). Technicians were trained to assist pharmacists in setting up their blood pressure station, measuring blood pressure values, administering BMQs and other self-report tools, confirming appointments, and rescheduling no-shows (without clerical assistance). Pharmacists were trained to identify and address the targeted barriers to medication adherence and blood pressure control using BMQs and other tools. Fourth, the participating corporations were contracted by the study director to implement the 6-month intervention at TEAM sites. Intervention teams received release time for training and generally scheduled one 2-hour blood pressure clinic per week during hours of overlapping staff, allowing them to focus on study patients. Participating corporations received modest compensation for documented interventions and training; patients received no compensation for keeping TEAM appointments. To address potential barriers to implementation, district managers and supervisors served on a protocol advisory group led by the study director</p> <p>Control: PATIENT INFORMATION ONLY Control participants received patient information only, including a 14-page guide for lowering blood pressure, pamphlet about hypertension in black patients, cards showing their blood pressure at baseline and follow-up interviews, and instructions to seek immediate medical care for a blood pressure value greater than 210/115 mm Hg at 6- or 12-month follow-up. Primary care physicians received an introductory letter; Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). guidelines<sup>25</sup>; and names of eligible patients. Pharmacy staff received a study description, posters, interest forms, JNC-7 guidelines, and no additional tools or training.</p>
Outcomes	<p>Adherence measure: Pharmacy refill measure Pharmacy corporations retrieved electronic refill data from centralized records for 522 patients (90.6%) who filled 8,991 antihypertensive medication prescriptions at any of their locations during months 1 through 12. Using refill dates and days supplied for each refill, we characterized every day as having available any major antihypertensive medication.</p>

	<p>Patient outcome: BP change</p> <p>The primary clinical outcomes were changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and proportion of patients achieving blood pressure below 140/90 mm Hg after 6 months (end of intervention) and 12 months (6 months after intervention discontinuation). The University of Wisconsin Survey Center (UWSC) was contracted by the study director (B.L.S.) to relocate all patients and perform the 6- and 12-month interviews according to protocol. UWSC is nationally recognized for state-of-the-art methods of tracking, relocating, and interviewing participants in longitudinal studies (<a href="http://www.uwsc.wisc.edu">www.uwsc.wisc.edu</a>). UWSC interviewers were blinded to pharmacy allocation, were not involved in recruitment or intervention, and were trained by an investigator (J.M.K.) to obtain three blood pressure readings using the same monitor and AHA guidelines used at baseline. The second and third readings were averaged and used in analyses.</p>
Notes	

Tinsel (2013)	
Methods	Randomised controlled trial
Participants	<p>The study location was GP practices in Southwest Germany.</p> <p>552 participants were randomized to the intervention group and 568 participants were randomized to the control group</p> <p>The eligibility criteria for GPs were (1) location in Southwest Germany, (2) offering the full spectrum of a family doctor's health care services and (3) nonparticipation in another study implementing an SDM training as intervention. There were no other inclusion or exclusion criteria for GP practices. Most of the participating GPs belonged to teaching practices associated with the Division of General Practice of the University Medical Centre Freiburg (Germany). Inclusion criteria for patients to be screened at T0 were (1) repeated prescription of antihypertensive medication, (2) age of at least 18 years, (3) insured by a statutory health fund with the exception of 'Bundesknappschaft and See-health insurance', and (4) understanding of the German language. Exclusion criteria were dementia, mental handicap, or short life expectancy. There were no other inclusion or exclusion criteria for patients.</p>
Intervention	<p>Intervention: SHARED DECISION-MAKING</p> <p>Those GPs who had been allocated to the intervention group took part in an SDM training programme [26] which had been evaluated in various studies [22,23,38,39]. It was adapted to the requirements of antihypertensive treatment in general practice and entailed six</p>

	<p>hours in total. The training included the following elements: (1) information on arterial hypertension, (2) physician-patient communication and risk communication, (3) the process steps of SDM, (4) motivational interviewing [40,41], (5) introduction of a decision table listing options to lower CVR, and (6) use of case vignettes for role plays simulating physician-patient consultations. Additionally, we recommended implementing a cardiovascular risk calculator for GPs which included elements of SDM [24,42]. Furthermore we delivered patient information flyers [43] to the GPs of the intervention group. The intervention took place before the T1 data assessment</p> <p>Control: USUAL CARE GPs of the control group treated their patients as usual.</p>
Outcomes	<p>Adherence measure: Self-report MARS-D Self report in each of the four data collections, questionnaires were distributed to the patients by their GP practices</p> <p>Patient outcome: BP 24-hour ambulatory blood pressure monitoring (ABPM) was conducted.</p> <p>Cardiovascular risk score Cholesterol and HbA1c were assessed by GP practices so CVR could be calculated.</p>
Notes	

Wong (2013)	
Methods	Randomised controlled trial
Participants	<p>The study location was a designated public, primary care clinic, New Territories East region, Hong Kong, China.</p> <p>113 participants were randomized to the intervention group and 161 participants were randomized to the control group</p> <p>Patients who attended the designated clinic were eligible if they were (1) aged 18 years or older; (2) taking at least one long-term antihypertensive agents; (3) not previously received any community-based intervention programs on medication adherence; and (4) evaluated as having suboptimal compliance to the antihypertensive medication, as assessed by the Morisky self-reported adherence questionnaire. The exclusion criteria include (1) inability of the patient to communicate and understand Cantonese and (2) the presence of medical conditions rendering the patient not mentally capable to participate in this study.</p>

Intervention	<p><b>Intervention: PHARMACIST COUNSELLING</b></p> <p>Participants received both usual care followed by community-based medication counseling service immediately after physician consultation. The counseling took place in a consultation room in the same clinic, where the pharmacists counseled the patients resembling their medication adherence intervention in the community. The service is delivered by community pharmacists from a Non-Governmental Organization, including: (1) addressing participants' concern and uncertainties in taking medications; (2) reinforcing relevant knowledge on the chronic diseases they are suffering from; (3) education on the proper methods to take their medications, including drug taking dosage, frequency and special precautions if applicable; and (4) provision of medication knives and pill boxes as judged necessary by the pharmacist. Most of the sessions lasted for 15–20 minutes, and all interventions were tailored- made to the specific needs of each patient. Participant goals designed to enhance antihypertensive medication adherence referred to the measurement of the Morisky self-reported adherence questionnaire scores. They received comprehensive pamphlets summarizing the content of medication counseling and were motivated to enhance compliance to antihypertensive agents. All participants in this group were offered free-of-charge telephone consultations with community pharmacists within the study period. All community pharmacist interventions were standardized according to content and format. To avoid inter-pharmacist variations, only one pharmacist conducted all interventional sessions at baseline throughout the study</p> <p><b>Control: USUAL CARE</b></p> <p>Participants assigned to the usual care group were educated on their diagnoses of hypertension, their implications, and discussed on the importance of proper medication compliance to control hypertension by the attending physicians. Most of these sessions lasted for 2–3 minutes, resembling real clinical practice.</p>
Outcomes	<p><b>Adherence measure: Self-report</b></p> <p>Self-reported medication adherence was measured by the eight-item Morisky Medication Adherence Scale (MMAS-8). The MMAS-8 has been proven reliable (a <math>\frac{1}{4}</math> 0.83) for assessment of adherence in patients with hypertension, and is significantly associated with blood pressure control.<sup>22–24</sup> Using a cut-off of 6, its sensitivity or identifying lower versus higher adherers was estimated to be 93% and the specificity was 53%.<sup>23</sup> The MMAS-8 has been demonstrated to have good concurrent and predictive validity and might function as a screening tool in outpatient settings with different patient groups.<sup>23</sup> MMAS-8 scores can range from zero to eight in integers (see Appendix). The precise scoring criteria can be obtained from the developer/owner. The advantages of this instrument over other methods of measurement include its</p>

	<p>simplicity, quick administration and low- cost. A validated Chinese translation of the MMAS-825 was used and adapted specifically for antihypertensive agents in this study. The survey was in Cantonese, tailored-made for use in the Hong Kong population.</p> <p>Patient outcome: BP change</p> <p>Two 3-monthly visits were arranged for each participant. The measurements of the Morisky scores, systolic blood pressure, and diastolic blood pressure were taken. Blood pressure (BP) was measured by a random-zero sphygmomanometer in the right arm with an appropriately sized cuff. After the potential participants rested in a sitting position for 5 minutes, the physician measured the BP at least one hour after the subject's last meal and at least 30 minutes after smoking or consumption of a caffeinated beverage. Systolic BP is the appearance of the first Korotkoff sound, and diastolic BP is the disappearance of the fifth Korotkoff sound. The researchers who conduct these measurements were blinded to the group allocated, and all BP levels recorded were rounded to the nearest 1 mmHg.</p>
Notes	

## Appendix VI: Risk of bias in included studies

Amado 2011	Risk of bias	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information about sequence generation. “The study was designed as multi-centre, prospective, cluster randomised, controlled clinical trial, using the primary healthcare centre as a randomization unit.” (pg 63)
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described. “The study was designed as multi-centre, prospective, cluster randomised, controlled clinical trial, using the primary healthcare centre as a randomization unit.” (pg 63)
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Most adherence measures were by self report (pg 66). Authors mention the possibility of contamination between intervention and control groups
Blinding of outcome assessment (detection bias) Adherence measure	Unclear risk	(PRIMARY) SELF REPORT - QUESTIONNAIRES - Not stated whether the nurses collecting the data were blinded
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE -Not stated whether nurse collecting data was blinded
Blinding of participants (performance bias) Adherence measure	Unclear risk	(PRIMARY) BMI - Not stated whether nurse collecting data was blinded
Blinding of participants (performance bias) Patient outcome	Unclear risk	(PRIMARY) SELF REPORT – QUESTIONNAIRES - subjective outcome; no mention of blinding
Blinding of personnel (performance bias) Adherence measure	Unclear risk	(PRIMARY) BMI -No blinding of other study personnel mentioned
Blinding of personnel (performance bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE - No blinding of other study personnel mentioned
Incomplete outcome data (attrition bias) Adherence measure	Low risk	(PRIMARY) SELF REPORT - QUESTIONNAIRES - Reasons for dropouts were similar in both groups
Incomplete outcome data (attrition bias) Patient outcome	Low risk	(PRIMARY) BMI - Reasons for dropouts similar in both

Incomplete outcome data (attrition bias)	Low risk	(PRIMARY) BLOOD PRESSURE - Reasons for dropouts similar in both groups
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<b>Baird 1984</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No discussion of randomization process. "Patients were allocated randomly" (pg 96)
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment. "Patients were allocated randomly" (pg 96)
Selective reporting (reporting bias)	Unclear risk	Unclear. No protocol available
Other bias	Unclear risk	Not enough details provided in the article
Blinding of outcome assessment (detection bias) Adherence measure	Unclear risk	(PRIMARY) PILL COUNT -No mention of blinding of study staff
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE AND HEART RATE - No information is provided in the article on blinding
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) PILL COUNT -No blinding and outcome is possibly affected
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE AND HEART RATE - No information is provided in the article, but non-blinding of the patient is unlikely to affect this outcome
Blinding of personnel (performance bias) Patient outcome	Unclear risk	(PRIMARY) PILL COUNT -No mention of blinding of study staff
Blinding of personnel (performance bias) Adherence measure	Unclear risk	(PRIMARY) BLOOD PRESSURE AND HEART RATE - No mention of blinding of staff
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	(PRIMARY) PILLCOUNT-Unclear how many patients withdrew from this portion of the trial, otherwise reasons for dropouts are provided in Table 3
Incomplete outcome data (attrition bias)	Unclear risk	(PRIMARY) BLOOD PRESSURE AND

Patient outcome		HEART RATE - Unclear how many patients withdrew from this portion of the trial, otherwise reasons for dropouts are provided in Table 3
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<b>Becker 1986</b>	<b>Risk of bias</b>	
Bias		
Random sequence generation (selection bias)	Unclear risk	Method not described in the article. (pg 358) "Patients who agreed were randomly assigned into either the experimental or the control group."
Allocation concealment (selection bias)	Unclear risk	(pg 358) "Patients who agreed were randomly assigned into either the experimental or the control group..." No description of allocation concealment
Selective reporting (reporting bias)	Unclear risk	Probably all outcomes reported, but insufficient information in the article to judge
Other bias	Low risk	Authors identify possible co-intervention effect, but similar in both arms, so unlikely to have introduced bias. (pg 361) "The magnitude of this cointervention effect is suggested by the increase in the proportion of patients in both groups whose (...) pressure was controlled between the time of the pre-enrollment and the baseline visit (i.e. before the special packaging intervention was initiated)." This co-intervention appears to have affected both groups equally and is thus unlikely to have biased the results
Blinding of outcome assessment (detection bias) Adherence measure	Unclear risk	(PRIMARY) SELF REPORT - INTERVIEW - Unclear if nurses were blinded. (pg 358) "All data collection was done by a nurse research assistant immediately before a regular office visit. Physicians caring for these patients were aware that compliance study was in progress but were not told the aims of the study or informed of whether any individual patient was in the experimental or control group."
Blinding of outcome	Low risk	(PRIMARY) BLOOD PRESSURE -

assessment (detection bias) Patient outcome		Blinding. (pg 358) “Physicians caring for these patients were aware that a compliance study was in progress but were not told the aims of the study or informed of whether any individual patient was in the experimental or control group.”
Blinding of participants (performance bias) Adherence measure	High risk	((PRIMARY) SELF REPORT - INTERVIEW - No blinding and likely to affect the outcome
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - Patients not blinded but likely would not impact outcome
Blinding of personnel (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - Physicians were blinded. (pg 358) “Physicians caring for these patients were aware that compliance study was in progress but were not told the aims of the study or informed of whether any individual patient was in the experimental or control group.”
Blinding of personnel (performance bias) Adherence measure	Unclear risk	(PRIMARY) SELF REPORT - INTERVIEW- Physicians were blinded. (pg 358) “All data collection was done by a nurse research assistant immediately before a regular office visit. Physicians caring for these patients were aware that compliance study was in progress but were not told the aims of the study or informed of whether any individual patient was in the experimental or control group.”
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	(PRIMARY) SELF REPORT - INTERVIEW- Not enough information to judge. We do not know to which arm the drop outs belong. (pg 359) “Most of these patients did not show up for appointments and could not be contacted by telephone. Other reasons for dropouts included death (1) and discontinuation of medications (1) . No patients indicated that problems with the medication packaging were involved

		in their reasons for dropping out.”
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE – Not enough information to judge. We do not know to which arm the dropouts belong. (pg 359) “Most of these patients did not showup for appointments and could not be contacted by telephone. Other reasons for dropouts included death (1) and discontinuation of medications (1). No patients indicated that problems with the medication packaging were involved in their reasons for dropping out.”

<b>Dusing 2009</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention of randomization methods. (pg 895) “... cluster-randomized (by center), open-label, multicenter parallel-group study... Centers were assigned to one of the following two treatment arms in a ratio of 1 : 1, centers providing their patients with supportive measures and centers not providing their patients with supportive measures. To avoid any investigator bias in treating one patient with and another patient without supportive measures, investigators rather than patients were randomized to provide only treatment with or without supportive measures for all patients at a single participating center.”
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment. (pg 895) “...cluster- randomized (by center), open-label, multicenter parallel-group study... Centers were assigned to one of the following two treatment arms in a ratio of 1 : 1, centers providing their patients with supportive measures and centers not providing their patients with supportive measures. To avoid any investigator bias in treating one patient with and another patient without supportive measures, investigators rather than patients were randomized to provide only treatment with or without supportive measures for all patients at a single participating center.”
Selective reporting	Unclear risk	None detected but protocol not available

(reporting bias)		
Other bias	Unclear risk	No clear other biases and no limitations mentioned in article
Blinding of outcome assessment (detection bias) Adherence measure	Low risk	(PRIMARY)MEMS - Outcome not likely to be affected by outcome assessors
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE AND NORMALIZATION - Method of data collection not detailed in the article and no mention of blinding
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY)MEMS - Patients aware of intervention and the measure
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE AND NORMALIZATION - Patients not being blinded is unlikely to affect this outcome
Blinding of personnel (performance bias) Adherence outcome	Low risk	(PRIMARY)MEMS - It seems other staff were blind. (pg 896) "The centers providing standard care were blinded with regard to the content of the 'supportive measures'"
Blinding of personnel (performance bias) Patient measure	Low risk	(PRIMARY) BLOOD PRESSURE AND NORMALIZATION - Other staff were blinded. (pg 895) "The centers providing standard care were blinded with regard to the content of the 'supportive measures'." Also, open label but cluster RCT and objective outcome
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	(PRIMARY)MEMS - Uneven loss to follow-up and not all reasons for dropout are clear; adverse events was one reason for dropouts
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE AND NORMALIZATION- Uneven loss to follow-up and not all reasons for dropout are clear; adverse events was one reason for dropouts

<b>Friedberg 2014</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization was performed by the research coordinator, who was neither involved in assessment nor counselling. Random assignment was made by computer-generated randomization (using statistical analysis

		system) to each treatment group by permuted blocks of size 6 by the site. For all consecutive blocks of size 6 in a site, 2 subjects were in each of the 3 treatments.
Allocation concealment (selection bias)	Low risk	randomized assignments were concealed and computer-generated randomization was performed by the research coordinator, who was neither involved in assessment nor counseling. Participants knew that we were evaluating whether telephone interventions improve hypertension management, but they did not know which active telephone arm they were in. Counselors knew the treatment assignments, but did not know the BP and adherence outcomes. Research assistants were blinded to treatment assignment.
Selective reporting (reporting bias)	Low risk	Reports are consistent with stated plan on analysis.
Other bias	Low risk	Participants were randomized equally to the counselors with the same call procedures for SMI and HEI such that each counselor conducted both HEI and SMI calls. Calls were recorded, and a random sample was assessed weekly for treatment fidelity by the PI, research coordinator, and counselors.
Blinding of outcome assessment (detection bias) Adherence measure	Low risk	<b>SELF-REPORT - QUESTIONNAIRE</b> Participants knew that we were evaluating whether telephone interventions improve hypertension management, but they did not know which active telephone arm they were in. Counselors knew the treatment assignments, but did not know the BP and adherence outcomes. Research assistants were blinded to treatment assignment
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	<b>BP CONTROL AT 6 MONTHS</b> Participants could not be fully blinded but blinding is unlikely to have affected this outcome. Objective measure from patient's point of view.

Blinding of outcome assessment (detection bias) Patient outcome	Low risk	<b>SYSTOLIC BLOOD PRESSURE</b> Participants could not be fully blinded but blinding is unlikely to have affected this outcome. Objective measure from patient's point of view.
Blinding of participants (performance bias) Adherence measure	High risk	<b>SELF-REPORT - QUESTIONNAIRE</b> Subjective measure. Patients were partially blinded (i.e., were blind as to which intervention arm they were in) but were aware that they had been allocated to an intervention group.
Blinding of participants (performance bias) Patient outcome	Low risk	<b>BP CONTROL AT 6 MONTHS</b> Participants knew that we were evaluating whether telephone interventions improve hypertension management, but they did not know which active telephone arm they were in. Counselors knew the treatment assignments, but did not know the BP and adherence outcomes. Research assistants were blinded to treatment assignment.
Blinding of participants (performance bias) Patient outcome	Low risk	<b>SYSTOLIC BLOOD PRESSURE</b> Participants knew that we were evaluating whether telephone interventions improve hypertension management, but they did not know which active telephone arm they were in. Counselors knew the treatment assignments, but did not know the BP and adherence outcomes. Research assistants were blinded to treatment assignment.
Blinding of personnel (performance bias) Adherence outcome	Low risk	<b>SELF-REPORT - QUESTIONNAIRE</b> Study personnel were blinded to study group and unlikely blinding could have been broken.
Blinding of personnel (performance bias) Patient measure	Low risk	<b>BP CONTROL AT 6 MONTHS</b> Personnel were blinded to treatment assignment and this was unlikely to be broken.
Blinding of personnel (performance bias) Patient measure	Low risk	<b>SYSTOLIC BLOOD PRESSURE</b> Personnel were blinded to treatment assignment and this was unlikely to be broken.
Incomplete outcome	Low risk	<b>SELF-REPORT - QUESTIONNAIRE</b>

data (attrition bias) Adherence measure		52 patients lost to follow-up Although this missing data percentage is small, to ensure study validity in case data are not missing completely at random, authors used a generalized estimating equations approach that yields unbiased estimates, if the missing data are missing at random.
Incomplete outcome data (attrition bias) Patient outcome	Low risk	BP CONTROL AT 6 MONTHS <10% attrition. Although this missing data percentage is small, to ensure study validity in case data are not missing completely at random, authors used a generalized estimating equations approach that yields unbiased estimates, if the missing data are missing at random.
Incomplete outcome data (attrition bias) Patient outcome	Low risk	SYSTOLIC BLOOD PRESSURE <10% attrition. Although this missing data percentage is small, to ensure study validity in case data are not missing completely at random, authors used a generalized estimating equations approach that yields unbiased estimates, if the missing data are missing at random.

<b>Friedman 1996</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description regarding random sequence generation. (pg 286) “after which participants were randomly assigned to either the TLC or usual care groups using a paired randomization protocol”
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment. (pg 286) “... after which participants were randomly assigned to either the TLC or usual care groups using a paired randomization protocol. The field technicians were blinded to the group assignments...”

Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	No major biases noted in the discussion but insufficient information provided to make a judgment
Blinding of outcome assessment (detection bias) Adherence measure	Unclear risk	(PRIMARY) PILL COUNT - Unclear if data collectors were blinded the entire study. (pg 286) “The field technicians were blinded to the group assignments until after baseline measurements were complete.. .”
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE - Unclear if data collectors blinded the entire study. (pg 286) “The field technicians were blinded to the group assignments until after baseline measurements were completed”
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) PILL COUNT - Patients not likely to be blind due to the nature of the intervention
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - Lack of blinding of the study participant is unlikely to affect this outcome
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	(PRIMARY) PILL COUNT –No mention of blinding of other study staff
Blinding of personnel (performance bias) Patient measure	Unclear risk	(PRIMARY) BLOOD PRESSURE - No mention of blinding study personnel
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	(PRIMARY) PILL COUNT - The attrition rate for the TLC group was 15% (n = 23), and for the usual care group it was 8% (n = 11). TLC group lost double patients to attrition than usual care. Not sure if that could have induced a change in the result
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE - The attrition rate for the TLC group was 15% (n = 23), and for the usual care group it was 8% (n = 11). TLC group lost double patients to attrition than usual care. Not

		sure if that could have induced a change in the result
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<b>Girvin 1999</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization. (pg 1628) "Randomization was conducted by an independent advisor (by resampling without replacement) after the placebo run-in period."
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment, though reference to an "independent advisor" may have meant allocation was concealed from study staff. (pg 1628) "Randomization was conducted by an independent advisor (by resampling without replacement) after the placebo run-in period. "
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	No biases noted in discussion, no other obvious risks of bias in study
Blinding of outcome assessment (detection bias) Adherence measure	High risk	(PRIMARY) PILL COUNT - (pg 1628) "The study could not be double-blind since an important outcome was the difference in compliance between the once daily and twice daily regimens. However, the investigator responsible for analysing the results was blinded as to the treatment phase."
Blinding of outcome assessment (detection bias) Adherence measure	High risk	(PRIMARY) MEMS - No mention of blinding outcomes assessors, but (pg 1628) "The study could not be double-blind since an important outcome was the difference in compliance between the once daily and twice daily regimens. However, the investigator responsible for analysing the results was blinded as to the treatment phase."
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - (pg 1628-9) "Blood pressure was measured at each visit using the Hawksley Random-Zero Sphygmomanometer
Blinding of participants	High risk	(PRIMARY)MEMS - Patients would

(performance bias) Adherence measure		have been aware that their pills were being tracked
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) PILL COUNT - Patients would have been aware that their pills were being counted
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - (pg 1628-9) “Blood pressure was measured at each visit using the Hawksley Random-Zero Sphygmomanometer (Lancing, UK)
Blinding of personnel (performance bias) Adherence outcome	High risk	(PRIMARY) MEMS - (pg 1628) “The study could not be double-blind since an important outcome was the difference in compliance between the once daily and twice daily regimens. However, the investigator responsible for analysing the results was blinded as to the treatment phase.”
Blinding of personnel (performance bias) Adherence outcome	High risk	(PRIMARY) PILL COUNT - (pg 1628) “The study could not be double-blind since an important outcome was the difference in compliance between the once daily and twice daily regimens. However, the investigator responsible for analysing the results was blinded as to the treatment phase.”
Blinding of personnel (performance bias) Patient measure	Low risk	(PRIMARY) BLOOD PRESSURE - (pg 1628) “Blood pressure was measured at each visit using the Hawksley Random-Zero Sphygmomanometer (Lancing, UK).”
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	(PRIMARY) PILL COUNT - No mention of groups missing data were from. (pg 1629) “Twenty-seven patients were recruited into the study, two of whom had to be withdrawn after experiencing headache, nausea and dizziness upon commencing enalapril therapy. The remaining 25 patients completed.”
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE – No mention of groups missing data were from. (pg 1629) “Twenty-seven patients were

		recruited into the study, two of whom had to be withdrawn after experiencing headache, nausea and dizziness upon commencing enalapril therapy. The remaining 25 patients completed
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<b>Greer 2014</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized using a block design based on participants' baseline Hill-Bone Compliance to High Blood Pressure Therapy (HBCHBPT) scale 16 scores. The HBCHBPT scale ranges from 14 (perfect adherence) to 56 (nonadherent), with a range of 42. A cutoff score of 22 (which is half of the range, 42) was used to distinguish high and low adherence. The author selected participants for the intervention and control groups by dividing the scores above and below 22 and randomly drawing participants for each block. "Randomly drawing" does not give enough information for a judgement.
Allocation concealment (selection bias)	High risk	Not reported but the nature of the intervention would suggest that allocation could not be concealed. The author selected participants for the intervention and control groups by dividing the scores above and below 22 and randomly drawing participants for each block.
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	None reported.
Blinding of outcome assessment (detection bias) Adherence measure	High risk	SELF-REPORT - QUESTIONNAIRE No information provided but the nature of the intervention would suggest that staff could not have been blinded.
Blinding of outcome assessment (detection bias) Patient outcome	High risk	BLOOD PRESSURE CONTROL No information provided but the nature of the intervention would suggest that staff could not have been blinded.
Blinding of participants	High risk	SELF-REPORT - QUESTIONNAIRE

(performance bias) Adherence measure		No information provided but the nature of the intervention would suggest that participants could not have been blinded.
Blinding of participants (performance bias) Patient outcome	High risk	BLOOD PRESSURE CONTROL No information provided but the nature of the intervention would suggest that participants could not have been blinded.
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	SELF-REPORT - QUESTIONNAIRE No information provided
Blinding of personnel (performance bias) Patient measure	Unclear risk	BLOOD PRESSURE CONTROL No information provided
Incomplete outcome data (attrition bias) Adherence measure	Low risk	SELF-REPORT - QUESTIONNAIRE There was no incomplete outcome data reported.
Incomplete outcome data (attrition bias) Patient outcome	Low risk	BLOOD PRESSURE CONTROL There was no incomplete outcome data reported.

<b>Haynes 1976</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Minimization used. (pg 1265) "39 such men were allocated by "minimisation" either to a control group or to an experimental group. Minimisation allows the simultaneous consideration of a large series of matching characteristics when allocating subjects to experimental and control groups, there by minimising (using randomisation in the case of ties) between group differences. The method is immune to experimenter bias and has been shown to substantially outperform simple randomisation in reducing the imbalance between treatment groups that has troubled several earlier randomised trials."
Allocation concealment (selection bias)		Minimization used. (pg 1265) "39 such men were allocated by "minimisation" either to a control group or to an experimental group. Minimisation allows the simultaneous consideration of a large series of matching characteristics

		when allocating subjects to experimental and control groups, there by minimising (using randomisation in the case of ties) between group differences. The method is immune to experimenter bias and has been shown to substantially outperform simple randomisation in reducing the imbalance between treatment groups that has troubled several earlier randomised trials.”
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Possible confounding bias identified by the authors in the Discussion portion of the paper. (pg 1268) “We are not satisfied, however, that this investigation is free from a fourth potential source of bias, and this is the confounding of the compliance- improving strategies with the amount of attention shown to these patients. By design, phase-II experimental patients received more attention (five hours, spread over six months) than phase-II controls, and our review of the compliance literature suggests that simply spending more time with patients, regardless of the content of the interchange, is associated with increased compliance.”
Blinding of outcome assessment (detection bias) Adherence measure	Low risk	(PRIMARY) PILL COUNT - Blinding was accounted for. (pg 1266) “At the end of phase 2 (in the twelfth month of treatment) patients were evaluated both at home and at the mill by examiners who were ”blind“ to their experimental group allocation.”
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - Outcome assessors were blinded to treatment group. (pg 1266) “At the end of phase II (in the twelfth month of treatment) patients were evaluated both at home and at themill by examiners who were ”blind“ to their experimental group allocation.”
Blinding of participants (performance bias) Adherence measure	Low risk	(PRIMARY) PILL COUNT - Pill count done unobtrusively once, while patient not in room. (pg 1266) “...The home visitor verified each patient’s doses while the patient was supplying a urine specimen (requested without prior

		warning), did an unobtrusive pill- count and compared it with a baseline established one month earlier.”
Blinding of participants (performance bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE - Patient blinding is not reported
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	(PRIMARY) PILL COUNT –No mention of blinding other study personnel
Blinding of personnel (performance bias) Patient measure	Low risk	(PRIMARY) BLOOD PRESSURE - Blinding of the outcome assessor is accounted for. (pg 1266) “At the end of phase II (in the twelfth month of treatment) patients were evaluated both at home and at the mill by examiners who were ”blind“ to their experimental group allocation.”
Incomplete outcome data (attrition bias) Adherence measure	Low risk	(PRIMARY) PILL COUNT - There are few missing outcome data; reason for missing data unrelated to intervention. (pg 1266) “1 control developed deep vein thrombosis and his hypotensive drugs were stopped; this patient was removed from the study, leaving 20 experimental patients and 18 controls.”
Incomplete outcome data (attrition bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - There are few missing outcome data; reason for missing data unrelated to intervention. (pg 1266) “1 control developed deep vein thrombosis and his hypotensive drugs were stopped; this patient was removed from the study, leaving 20 experimental patients and 18 controls.”

<b>Hosseinasab 2014</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Balanced block randomization was used to allocate patients to the study groups. Two of the authors (A.S. and Z.J.) had access to the randomization list, and they were not involved in the recruitment process at the clinic. The author who recruited patients (M.H.) used telephone calls to ask for an allocation order after a patient signed the informed consent.
Allocation concealment	Unclear risk	Insufficient information to permit high

(selection bias)		or low risk judgement.
Selective reporting (reporting bias)	Low risk	Protocol isn't available. Reporting of results consistent with plan of analysis noted in NCT01525108.
Other bias	Unclear risk	Study authors could not assess baseline adherence by pill counting method, and a translated version of Morisky scale was used in a subsample of patients to document baseline status. However, the translated version has not been validated in an Iranian population. Despite the limitations to the Morisky scale tool, the baseline BP of the study population could also confirm patients' inadequate adherence at the recruitment time (i.e., systolic BP: 144.4±7.4 vs. 145.9±6.4mm Hg; diastolic BP: 85.5±6.9 vs. 85.1±7.7mm Hg). We should also mention that the pill-counting method also possesses some intrinsic disadvantages, as mentioned in the previous paragraphs; nevertheless, it remains one of the most common adherence measurement tools.
Blinding of outcome assessment (detection bias) Adherence measure	Low risk	<b>PILL COUNT</b> The outcome not likely to be influenced by lack of blinding. The pill counting was carried out in a separate room not exposed to the medial care team.
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	<b>BLOOD PRESSURE</b> Outcome unlikely to be affected by blinding
Blinding of participants (performance bias) Adherence measure	Unclear risk	<b>PILL COUNT</b> Not reported.
Blinding of participants (performance bias) Patient outcome	Unclear risk	<b>BLOOD PRESSURE</b> Not reported
Blinding of personnel (performance bias) Adherence outcome	High risk	<b>PILL COUNT</b> Subjective measure as the patients would be aware of the need to take their pills. We used pill counting to assess patients' drug use at the baseline, as per the study protocol. After trying the pill counting on several recruited patients, we realized that the method was inaccurate and

		unreliable because the number of prescribed and consumed pills before recruitment could not be evaluated by the investigator. Hence we discontinued the pill counting at the baseline. To have an indication of drug use at the baseline, we used a translated version of the Morisky Medication Adherence Scale 8 (Morisky scale) on a random subsample of remaining patients (the translation had not been validated). Because the pill counting proved unreliable for assessing the baseline drug use, the results of applying Morisky scale on a random subsample of patients (n = 87) suggested that 56.3% of the patients had low or moderate adherence to drug use
Blinding of personnel (performance bias) Patient measure	Low risk	BLOOD PRESSURE Objective measure. Outcome unlikely to be affected by blinding.
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	PILL COUNT Insufficient information to allow judgement
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk	BLOOD PRESSURE Insufficient information to make judgement.

<b>Johnson 1978</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not enough information given in the article. (pg 1035) Once their informed consent was obtained the subjects were stratified for age (less than 45 years old and 45 or older) and sex, then assigned at random to one of 4 groups in a 2 x 2 factorial design: (1) self recording and monthly home visits; (2) self recording only; (3) monthly home visits; and (4) neither self recording nor monthly home visits
Allocation concealment (selection bias)	Unclear risk	Not enough information given in the article. (pg 1035) Once their informed

		consent was obtained the subjects were stratified for age (less than 45 years old and 45 or older) and sex, then assigned at random to one of 4 groups in a 2 x 2 factorial design: (1) self recording and monthly home visits; (2) self recording only; (3) monthly home visits; and (4) neither self recording nor monthly home visits
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	None noted but unclear
Blinding of outcome assessment (detection bias) Adherence measure	Unclear risk	(PRIMARY) SELF REPORT - INTERVIEW - Adherence data were collected at subject's residence by an investigator, most likely unblinded. (pg 1035) "Six months later all subjects were visited twice within 1 to 3 days by the visitor who had previously seen them. Standardized blood pressure measurements were made and compliance with therapy was assessed by interview and pill count (the percentage of prescribed pills that had been consumed was estimated by comparing pills on hand with prescription records of pills dispensed and the regimen prescribed)."
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE – No mention of blinding
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) SELF REPORT - INTERVIEW - Participants would have been aware of their group membership
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - Blood pressure unlikely to be influenced by patient blinding
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	(PRIMARY) SELF REPORT - INTERVIEW - Blinding measures not described except for the independent investigator measuring BP. Other personnel may be unblinded
Blinding of personnel (performance bias) Patient measure	Unclear risk	(PRIMARY) BLOOD PRESSURE - No mention of blinding
Incomplete outcome	Low risk	(PRIMARY) SELF REPORT -

data (attrition bias) Adherence measure		INTERVIEW- Small rate of attrition - 4/140. Reasons for the missing data unlikely to be connected with outcome
Incomplete outcome data (attrition bias) Patient outcome	Low risk	(PRIMARY) BLOODPRESSURE - Small rate of attrition - 4/140. Reasons for the missing data unlikely to be connected with outcome

<b>Ma 2013</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	When the eligible participants visited the outpatient department, they were asked to select an envelope to randomly allocate all of the 120 participants to the control or intervention group. The number one on the envelope indicated that the patient was in the control group, and the number two on the envelope assigned the patient to the intervention group. All of the participants were masked to the group assignment; however, the participating nurses were not blinded to the assignment. - Does not state if the envelope was opaque or sealed.
Allocation concealment (selection bias)	Low risk	All of the participants were masked to the group assignment; however, the participating nurses were not blinded to the assignment.
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	The sample size is very small, and 14 patients dropped out of the study. The missing cases most likely have an effect on the assessment of MI. The nurses who delivered the MI counselling and usual care were not blinded to the sample allocation. These nurses are acquainted with one another, which may bias the results. They used a self-reported tool to measure adherence rather than an objective measure, which can be biased by inaccurate patient recall or by the influence of social desirability.

Blinding of outcome assessment (detection bias) Adherence measure	High risk	SELF - REPORT - QUESTIONNAIRE Participating nurses were not blinded to the assignment.
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	BLOOD PRESSURE Nurses at the two community health centres took the BP of the patients during their outpatient visits in the two different phases of the study without joining the study.
Blinding of participants (performance bias) Adherence measure	Low risk	SELF - REPORT - QUESTIONNAIRE All of the participants were masked to the group assignment.
Blinding of participants (performance bias) Patient outcome	Low risk	BLOOD PRESSURE All of the participants were masked to the group assignment.
Blinding of personnel (performance bias) Adherence outcome	High risk	SELF - REPORT - QUESTIONNAIRE Study staff not blinded, could have had an effect on study outcome.
Blinding of personnel (performance bias) Patient measure	Low risk	BLOOD PRESSURE Nurses at the two community health centres took the BP of the patients during their outpatient visits in the two different phases of the study without joining the study.
Incomplete outcome data (attrition bias) Adherence measure	Low risk	SELF - REPORT - QUESTIONNAIRE Drop-out balanced across groups, reasons similar across groups.
Incomplete outcome data (attrition bias) Patient outcome	Low risk	BLOOD PRESSURE Drop out similar between groups, reasons for drop out similar between groups.

<b>Margolius 2012</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear method of randomization - (pg 200) "Study arm assignments were randomly ordered and enclosed in sealed, consecutively numbered envelopes. After enrollment, participants were assigned to one of the study arms by opening the next sealed envelope."

Allocation concealment (selection bias)	Low risk	Low bias method of allocation concealment - (pg 200) “Study arm assignments were randomly ordered and enclosed in sealed, consecutively numbered envelopes. After enrollment, participants were assigned to one of the study arms by opening the next sealed envelope.”
Selective reporting (reporting bias)	Unclear risk	In the protocol most outcomes other than adherence measure were mentioned (ref 20 - Bennett H, Laird K, Margolius D, Ngo V, Thom DH, Bodenheimer T. BMC Public Health 2009;9:456-61). The effectiveness of health coaching, home blood pressure monitoring, and home-titration in controlling hypertension among low-income patients: protocol for a randomized controlled trial
Other bias	High risk	The authors note the following limitations: the use of control, outcome measurement noted as limitations. (pg 204) “This study had several limitations. A usual-care arm would have been helpful to further substantiate the improvement in SBP found in both intervention arms. In recent studies involving patients with elevated baseline SBP levels, however, levels dropped by 2, 6, 7, 10, 12, and 14 mm Hg with usual care, reductions considerably smaller than the approximately 20-mm Hg SBP reduction in both groups of our study. In an effort to pattern our study intervention to standard clinical care, we used blood pressures measured by medical assistants at the office visit. This approach may have introduced more random error creating a bias toward not finding a difference between study arms. It is unlikely that it affected the result to the point of masking a true significant difference, however. The potential impact on the before-after analysis would be toward the null hypothesis, making our results a conservative estimate of actual change from baseline to 6 months. The association between number of coaching encounters and SBP reduction, while supportive of a true effect of health coaching, relied on

		observational data and could reflect confounding by unmeasured variables. Although we expected health coaching to improve medication adherence, self reported adherence decreased over the course of the study. Two factors may explain this seemingly paradoxical finding. First, on the basis of coaches' reports, many patients at baseline did not know their medications well enough to accurately report adherence. Second, patients may have become more truthful as they developed trusting relationships with their coaches. Also, self reported adherence correlates poorly with more objective adherence measures.”
Blinding of outcome assessment (detection bias) Adherence measure	Low risk	(PRIMARY) SELF REPORT - INTERVIEW- The outcome was self reported by the participants. The outcome was not likely to be affected by the lack of blinding of data collectors
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - No mention of blinding of outcome assessors but objective outcome - “. . .blood pressures were measured with an automated machine on 1 arm.”
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) SELF REPORT - INTERVIEW – Subjective outcome; no mention of blinding of patients
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - No mention of blinding but objective outcome - “. . .blood pressures were measured with an automated machine on 1 arm.”
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	(PRIMARY) SELF REPORT - INTERVIEW- No mention of blinding or of role of other study personnel in outcome assessment
Blinding of personnel (performance bias) Patient measure	Low risk	(PRIMARY) BLOOD PRESSURE - No mention of blinding of outcome assessors but objective outcome - “. . .blood pressures were measured with an automated machine on 1 arm.”
Incomplete outcome data (attrition bias) Adherence measure	Low risk	(PRIMARY) SELF REPORT - INTERVIEW – There were no significant differences in attrition rates between the 2 groups. Patients who dropped out or were lost to follow-up did not differ significantly

		from patients who completed the study
Incomplete outcome data (attrition bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - There were no significant differences in attrition rates between the 2 groups. Patients who dropped out or were lost to follow up did not differ significantly from patients who completed the study

<b>Marquez Contreras 2005</b>		<b>Risk of bias</b>
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The author notes that they used a random numbers table
Allocation concealment (selection bias)	Low risk	Centralized allocation. The “intervention group designation was carried out by two investigators not included as field investigators, and on a centralized basis.” No other description of allocation concealment is described. But marked low because the process of randomization was centralized, performed by 2 investigators not included as field investigators, away from the study sites
Selective reporting (reporting bias)	Low risk	The author notes, “...study explores whether the intervention is targeted to patients with hypertension, based on two strategies adapted to our setting (“telephone intervention” and “mail intervention”), is effective in improving compliance. This question answered in the study.”
Other bias	Low risk	The author notes that the population included in this study consists of newly diagnosed and uncontrolled hypertensive patients. These 2 populations are different, and indeed there is a high percentage of uncontrolled hypertensive patients that could not be controlled because of poor adherence. Also, we should bear in mind that the generalization of these study findings excludes patients with previous acutemyocardial infarction seen in primary care centers
Blinding of outcome	Low risk	PRIMARY) PILL COUNT - Those

assessment (detection bias) Adherence measure		collecting the data were stated to be blinded. “The field technicians were blinded to the group assignments until after the baseline measurements were completed. Subjects assigned to the TLC intervention group were trained to use TLC and an automated sphygmomanometer. All participants received a final home visit 6 months after entry into the study when all study measurements were re-administered by technicians blinded to the study assignments.” (pg 286)
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE - Blinding of primary health physician not mentioned in the article. “The field technicians were blinded to the group assignments until after the baseline measurements were completed.” (pg 286)
Blinding of participants (performance bias) Adherence measure	Unclear risk	(PRIMARY) PILL COUNT - Patients would have been aware of the intervention. However, “at the follow-up and final visits, BP, weight and tablet count were recorded - the investigator being required to show discretion in counting the tablets, in order to avoid patient bias.”
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - This is an objective measure of outcome
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	(PRIMARY) PILL COUNT - No information on blinding given. There is insufficient information to permit judgment of ‘Low risk’ or ‘High risk’
Blinding of personnel (performance bias) Patient measure	Unclear risk	(PRIMARY) BLOOD PRESSURE - No information on blinding given. There is insufficient information to permit judgment of ‘Low risk’ or ‘High risk’
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	(PRIMARY) PILL COUNT - No information given about why the dropouts occurred
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE - Reasons for dropout were not given

<b>Marquez Contreras</b>	<b>Risk of bias</b>
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<b>2006</b>		
<b>Bias</b>	<b>Author judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Randomization done using random number table. (pg 170) “The patients were randomly assigned to one of the two groups, stratified by age and sex. The randomization process was centralized and blind, performed using random number tables and by a person not involved in the follow-up.”
Allocation concealment (selection bias)	Low risk	Allocation concealment completed. (pg 170) “The patients were randomly assigned to one of the two groups, stratified by age and sex. The randomization process was centralized and blind, performed using random number tables and by a person not involved in the follow-up.”
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	No mention of limitations in discussion or other clear biases
Blinding of outcome assessment (detection bias) Adherence measure	Unclear risk	(PRIMARY) MEMS - No mention of blinding of outcome assessors. (pg 174) “The methodology has been correct: a randomized, double-blind trial”
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT- Method of blinding not described but less likely to affect BP reading - electronic measurement. (pg 174) “The methodology has been correct: a randomized, double-blind trial”
Blinding of participants (performance bias) Adherence measure	Unclear risk	(PRIMARY) MEMS - No mention of blinding of patients. MEMS is obtrusive but objective measure. (pg 174) “The methodology has been correct: a randomized, double-blind trial”
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT - Objective outcome but no mention of blinding of patient
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	(PRIMARY) MEMS - Uncertain mention of blinding of study personnel. (pg 174) “The methodology has been correct: a randomized, double-blind trial”
Blinding of personnel (performance bias) Patient measure	Low risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT- Method of blinding not described but less likely to affect BP

		reading - electronic measurement. (pg 174) “The methodology has been correct: a randomized, double-blind trial”
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	(PRIMARY) MEMS - Usable sample size did not meet power calculations - 200 versus 250 (80% of power calculation). Missing data uniform across groups - 13 each. Statistically significant difference only in diastolic BP. Not sure whether the missing data and reduced sample size could have affected the result. (pg 171) “A total of 250 patients were included, with data being obtained from 226. Of these, compliance data were obtained in 200 subjects (88.49% of the sample), with 26 subjects withdrawing from the study, 13 from the GC and 13 from the IG (P ¼ NS). Four of these were as a result of adverse events, 10 because of travel or change of address, one because of the intention to become pregnant, one because of the detection of secondary AHT (CG), four did not attend the scheduled visits, and six withdrew as a result of the malfunctioning of the MEMS.”
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT - Usable sample size did not meet power calculations - 200 versus 250 (80% of power calculation). Missing data uniform across groups - 13 each. Statistically significant difference only in diastolic BP. Not sure whether the missing data and reduced sample size could have affected the result. (pg 171) “A total of 250 patients were included, with data being obtained from 226. Of these, compliance data were obtained in 200 subjects (88.49% of the sample), with 26 subjects withdrawing from the study, 13 from the GC and 13 from the IG (P ¼ NS). Four of these were as a result of adverse events, 10 because of travel or change of address, one because of the intention to become pregnant, one because of the detection of secondary AHT (CG), four did not attend the scheduled visits, and six

		withdrew as a result of the malfunctioning of the MEMS.”
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<b>Matsumura 2012</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomization was used. (pg 1416) ”Study treatments were allocated using a central, computer-based, randomization service accessible by the internet and telephone“
Allocation concealment (selection bias)	Low risk	Computerized randomization was used. (pg 1416) ”Study treatments were allocated using a central, computer-based, randomization service accessible by the internet and telephone“
Selective reporting (reporting bias)	Unclear risk	No protocol available; although it appears that everything was reported it is difficult to determine this without a protocol
Other bias	High risk	The authors note that ”...the present study was limited by the facts that there were not enough subjects and that the study period might not be sufficiently long enough to detect the small difference in adherence rates between the combination pill and control groups. In the present study, the patients were treated over 6 months. If the treatment period is to be longer, medication adherence might be improved in the combination pill group compared with the control group. Moreover, the present study provides little information regarding medication persistence. In order to achieve optimal outcomes in the treatment of hypertension, patients were required to take their medications not only properly (medication adherence) but also to continue to do so throughout long-term treatment (persistence).“ adherence rate is the selection bias of the patients participating in the present study, because all patients were screened for run-in phases 1 and 2. The patients with a low adherence rate might be excluded during run-in periods. Therefore, this excellent medication

		adherence rate observed in the present study might not be applicable to general Japanese hypertensive patients. In addition, many participants were not newly diagnosed hypertensive patients, but rather had been treated with antihypertensive drugs for several years. <sup>25</sup> Furthermore, a recent study demonstrated that merely participating in a clinical trial significantly increases adherence. <sup>26</sup> Even considering these limitations, however, the findings of the present study are largely new and provide important information on medication adherence regarding a combination pill of antihypertensive drugs” - p.1420-1421 “Electronic monitoring seems to be the most accurate method to evaluate medication adherence. <sup>27</sup> Unfortunately, however, the cost of this device precluded its use in the present study. Accordingly, the indirect method of pill counts was applied in the present study. This method can be applied to estimate the quantities of medications a patient presumably takes”. (pg 1421)
Blinding of outcome assessment (detection bias) Adherence measure	Unclear risk	(PRIMARY) PILL COUNT - No information on whether pill count was computerized. There is insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	(PRIMARY) BLOODPRESSURE -No information on whether the method of taking blood pressure was computerized. There is insufficient information to permit judgment of 'Low risk' or 'High risk'. Open trial
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) PILL COUNT - Open trial. Patients aware of allocation due to the nature of the intervention
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - This is an objective measure of outcome. Lack of blinding of patients is not likely to affect the end results
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	(PRIMARY) PILL COUNT -No information on blinding given. There is insufficient information to permit judgment of 'Low risk' or 'High risk'

Blinding of personnel (performance bias) Patient measure	Unclear risk	(PRIMARY) BLOOD PRESSURE -No information on blinding given. There is insufficient information to permit judgment of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) Adherence measure	Low risk	(PRIMARY) PILL COUNT - All patients were included in ITT analysis irrespective of completion. Overall, there was a high rate of completion
Incomplete outcome data (attrition bias) Patient outcome	Low risk	(PRIMARY)BLOOD PRESSURE -All patients were included in ITT analysis irrespective of completion. Overall, there was a high rate of completion

<b>Morgado 2011</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers were used. "Participants were allocated following simple randomisation procedures (equal allocation and without restrictions) using a computer-generated list of random numbers." (pg 133)
Allocation concealment (selection bias)	Low risk	The allocation sequence was concealed from the clinical pharmacist enrolling and assessing participants in sequentially numbered, opaque, sealed envelopes. The computer-generated the allocation sequence and the envelopes were prepared by a researcher with no clinical involvement in the trial
Selective reporting (reporting bias)	Low risk	The primary outcome measures with respect to pharmaceutical care efficacy were the proportion of patients achieving BP control and reduction in baseline SBP and DBP. The secondary outcome measure was antihypertensive medication adherence, which was determined in both arms by a pharmacist using a validated 5-item adherence scale, derived from the 4-item scale developed by Morisky et al
Other bias	Low risk	The study seems to be free of other types of bias
Blinding of outcome assessment (detection bias) Adherence measure	High risk	(PRIMARY) 5-ITEM VALIDATED QUESTIONNAIRE - The pharmacist was not blinded. "Pharmacists and physicians were aware of the patient

		allocated arm”. (pg 133)
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	(PRIMARY) PROPORTION OF PATIENTS WITH CONTROLLED BP - Nurses who were measuring blood pressure were blinded to group allocation
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) 5-ITEM VALIDATED QUESTIONNAIRE - “Based on the nature of the intervention, it is not feasible to blind hypertensive patients in pharmaceutical intervention models. Thus, whereas patients, pharmacists and physicians were aware of the patient allocated arm, nurses assessing BP were kept blinded to the allocation.” (pg 133)
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) PROPORTION OF PATIENTS WITH CONTROLLED BP - Lack of patient blinding unlikely to affect this outcome
Blinding of personnel (performance bias) Adherence outcome	High risk	(PRIMARY) 5-ITEM VALIDATED QUESTIONNAIRE - The pharmacist was not blinded. “Pharmacists and physicians were aware of the patient allocated arm”. (pg 133)
Blinding of personnel (performance bias) Patient measure	Unclear risk	(PRIMARY) PROPORTION OF PATIENTS WITH CONTROLLED BP - All personnel except nurses were unblinded. “Based on the nature of the intervention, it is not feasible to blind hypertensive patients in pharmaceutical intervention models. Thus, whereas patients, pharmacists and physicians were aware of the patient allocated arm, nurses assessing BP were kept blinded to the allocation.” (pg 133)
Incomplete outcome data (attrition bias) Adherence measure	Low risk	(PRIMARY) 5-ITEM VALIDATED QUESTIONNAIRE - Analysis with most ‘pessimistic’ outcome values for patients dropping out was done, conclusions did not change
Incomplete outcome data (attrition bias) Patient outcome	Low risk	(PRIMARY) PROPORTION OF PATIENTS WITH CONTROLLED BP - Only 3.6% of patients dropped out; intention-to-treat analyses did not change conclusions based on on-treatment analyses

<b>Ogedegbe 2012</b>	<b>Risk of bias</b>	
Bias	Author judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Used a computer random-number generator. "Separate randomization schedules were developed from a computerized random-number generator, balanced at set intervals, using permuted blocks in order to assure equal numbers in each arm. Randomization assignment was carried out by the study statistician using sealed envelopes. Upon randomization, each patient was entered into the study and included in the intention-to-treat analysis. A total of 95 patients were randomly assigned to each study group. As is typical for most behavioural interventions, neither the patient nor the RA delivering the motivational interviewing could be blinded to the intervention assignment. However, the primary-care physician did not know the randomization group to which his or her patient belonged." (pg 172s)
Allocation concealment (selection bias)	Unclear risk	There is no mention of sequential allocation but opaque and sealed envelopes used. "On completion of the baseline assessments, the study biostatistician randomly assigned patients to either the PE control group or the PA intervention group in a 1:1 ratio. Patient assignments were placed in sealed opaque envelopes. As is typical for most behavioural interventions, neither the patients nor the RAs were blinded to the intervention. The primary care providers did not know their patients' group assignment." (pg 323)
Selective reporting (reporting bias)	Low risk	The same measures were noted in the protocol. "Study measures included the Morisky self-report medication adherence questionnaire, the CES-D measure of depression, the Duke Social Support and Stress Scale (DUSOCS), the Charlson comorbidity index, the medication adherence self-efficacy scale (MASES), and the Treatment Self-Regulation questionnaire (TSRQ) measure of intrinsic motivation." (pg 173)
Other bias	Low risk	The study seems to be free of other types of bias

Blinding of outcome assessment (detection bias) Adherence measure	Low risk	(PRIMARY) ELECTRONIC PILL MONITOR – This is an objective measure of outcome
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT - “The primary care providers did not know their patients’ group assignments.” (pg 323)
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) ELECTRONIC PILL MONITOR - No patient blinding but blinding may have been broken due to the nature of the intervention
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT - The lack of blinding is not likely to affect the outcome. Information is also taken from patient records
Blinding of personnel (performance bias) Adherence outcome	Low risk	(PRIMARY) ELECTRONIC PILL MONITOR – This is an objective measure of outcome
Blinding of personnel (performance bias) Patient measure	Unclear risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT -No information on blinding given. There is insufficient information to permit judgment of ‘Low risk’ or ‘High risk’
Incomplete outcome data (attrition bias) Adherence measure	Low risk	(PRIMARY) ELECTRONIC PILL MONITOR - After randomization, 2 withdrew, 7 were unavailable to follow-up, and 3 died from the positive affect group, therefore 113 completed the trial from the intervention group. From the control group, 11 withdrew, and 5 were unavailable for follow-up. 115 completed the trial at 12 months from the control group. Refer to Figure, CONSORT diagram. Approximately same number of missing information is there from both groups and the follow-up at 12 months is greater than 80%
Incomplete outcome data (attrition bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT - After randomization, 2 withdrew, 7 were unavailable to follow-up, and 3 died from the positive affect group, therefore 113 completed the trial from the intervention group. From the control group, 11 withdrew, and 5 were unavailable for follow-up. 115 completed the trial at 12 months from

		the control group. Refer to Figure, CONSORT diagram. Approximately same number of missing information is there from both groups and the follow-up at 12 months is greater than 80%
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<b>Ogedegbe 2015</b>		<b>Risk of bias</b>
<b>Bias</b>	<b>Authors judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk of bias	<p>Randomization of Sites and Patient Recruitment Thirty CHCs were pairwise matched with respect to size, and within each matched pair one was randomly assigned to the intervention condition (IC) and the other to usual care (UC). Details of patient recruitment are reported elsewhere. 9 Patients who agreed to participate (via letters from their primary care clinicians) were invited to the CHC to meet with a trained research assistant who obtained informed consent and conducted the baseline visit to assess their BP with BpTRU (model BPM-300; MEG International Services Ltd, Coquitlam, British Columbia, Canada), a validated, automated oscillometric BP monitor. 10 From Fernandez_2011 The CAATCH trial has three nested levels of sampling: site, physician, and patient. Sites were matched for size (large/medium versus small), creating 15 matched pairs. Within each pair, one site was randomly assigned to IC and the other to UC. Due to a variety of unspecified factors, it was assumed that patients from the same site, and perhaps also patients having the same physician, would be somewhat more similar than randomly selected patients attending different CHCs or having different physicians. This implies correlated residuals due to 'clustered sampling,' that will be controlled in the primary outcome analysis by treating both CHC and clinician within CHC as random factors. Maximum likelihood estimates, approximate standard errors, and multi-</p>

		level modeling statistical tests for primary outcome analysis will be obtained using PROC MIXED (SAS) [25,26]. The comparison of treatment groups with respect to dichotomous or ordinal measures (e.g., gender or smoker) will be performed using the MIXOR software [27,28], which estimates a logistic regression (with random effects). The clustered sampling effects associated with CHC and physician will be adjusted for in the equation. As appropriate, the model will be further augmented to include both person-level covariates (e.g., gender) and time-varying covariates (e.g., body mass index). As stated, the primary hypothesis concerns the treatment by time interaction.
Allocation concealment (selection bias)	Unclear risk of bias	Allocation not described in sufficient detail to make judgement.
Selective reporting (reporting bias)	Low risk of bias	All outcomes mentioned in this paper are reported on. However, the protocol states that cost-effectiveness at 12 months is a secondary outcome and this is not reported on.
Other bias	Unclear risk of bias	Attrition rate of 30%, which is not uncommon for this underserved population. The second is a relatively low patient adherence to the various components on the intervention.
Blinding of outcome assessment (detection bias) Adherence measure	Low risk of bias	The primary care clinicians and study investigators were blinded to the study outcomes.
Blinding of outcome assessment (detection bias) Patient outcome	Low risk of bias	The primary care clinicians and study investigators were blinded to the study outcomes.
Blinding of participants (performance bias) Adherence measure	Unclear risk of bias	Not reported.
Blinding of participants (performance bias) Patient outcome	Unclear risk of bias	Not reported.
Blinding of personnel (performance bias) Adherence outcome	High risk of bias	Subjective measure.

Blinding of personnel (performance bias) Patient measure	Low risk of bias	Objective measure. Outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Adherence measure	Low risk of bias	Attrition and exclusions were reported.
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk of bias	Reasons for attrition not given Missing outcome data is not balanced across groups.

<b>Rudd 2004</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used a computer-generated random number randomization method. "After establishing eligibility, patients gave written informed consent and underwent randomization using computer-generated assignment." (pg 922)
Allocation concealment (selection bias)	Unclear risk	No information was provided about how allocation was handled
Selective reporting (reporting bias)	Unclear risk	No protocol available; although it appears that everything was reported it is difficult to determine this without a protocol
Other bias	Low risk	The study seems to be free of other types of bias
Blinding of outcome assessment (detection bias) Adherence measure	Unclear risk	(PRIMARY) ELECTRONIC DRUG EVENT MONITOR - Notes blinding of data collectors for other measures but not for MEMS
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - Outcome assessors blinded and semi-automated portable device used to measure BP. "Patients in both groups returned to the clinic at 3 and 6 months for BP measurements, which were performed by study staff blinded to group assignment." (pg 922)
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) ELECTRONIC DRUG EVENT MONITOR - Patients were probably unblinded due to the nature of intervention
Blinding of participants (performance bias)	Low risk	(PRIMARY) BLOOD PRESSURE - Objective

Patient outcome		measure unlikely to be influenced by lack of patient blinding
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	(PRIMARY) ELECTRONIC DRUG EVENT MONITOR - Notes blinding of study personnel for baseline and BP measures but not MEMS
Blinding of personnel (performance bias) Patient measure	Unclear risk	(PRIMARY) BLOOD PRESSURE – No information on blinding given. There is insufficient information to permit judgment of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) Adherence measure	Low risk	(PRIMARY) ELECTRONIC DRUG EVENT MONITOR - Reasons for dropouts provided; dropouts fairly similar across groups
Incomplete outcome data (attrition bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - Reasons for dropouts provided and dropouts similar in number across groups

<b>Sackett 1975</b>	<b>Risk of bias</b>	
Bias	Author judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described: “After stratification for factors likely to influence either compliance or the probability that their blood-pressure could be controlled (prior antihypertensive therapy, age, other illness, and severity of hypertension), they were randomly allocated into a factorial design which permitted the simultaneous evaluation of the ability of two independent strategies to enhance compliance with antihypertensive therapy.” (pg 1205)
Allocation concealment (selection bias)	Low risk	The author indicated allocation was concealed
Selective reporting (reporting bias)	Unclear risk	No protocol available; although it appears that everything was reported it is difficult to determine this without a protocol
Other bias	Low risk	The study seems to be free of other types of bias
Blinding of outcome	Low risk	(PRIMARY) PILL COUNT - The men

assessment (detection bias) Adherence measure		were re-assessed by staff who were unaware of the experimental group allocation (pg 1206)
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - Outcome assessors were blinded
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY) PILL COUNT - The author noted that the patients were not blinded
Blinding of participants (performance bias) Patient outcome	Low risk	(PRIMARY) BLOOD PRESSURE - The author has noted that the patients were not blinded but blinding would likely not impact outcome
Blinding of personnel (performance bias) Adherence outcome	Low risk	(PRIMARY) PILL COUNT - The men were re-assessed by staff who were unaware of the experimental group allocation (pg 1206)
Blinding of personnel (performance bias) Patient measure	Unclear risk	(PRIMARY) BLOOD PRESSURE - No information on whether the method of taking blood pressure was computerized. There is insufficient information to permit judgment of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	(PRIMARY) PILL COUNT - Reasons for dropouts were not provided
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE - Reasons for missing data were not provided

<b>Schroeder 2005</b>	<b>Risk of bias</b>	
Bias	Author judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomization; computer-generated numbers were used for randomization. "One of the authors (TJP) who was not involved in practice and patient recruitment randomized eligible patients stratified by age and sex to the intervention and control groups using computer-generated random numbers, which were assigned to an anonymized list of participants. The

		principal investigator (KS) passed the randomization schedule on to the practice nurses shortly before the appointment for delivering the intervention.” (pg 146)
Allocation concealment (selection bias)	Low risk	One author not involved in the rest of the study completed randomization. “One of the authors (TJP) who was not involved in practice and patient recruitment randomized eligible patients stratified by age and sex to the intervention and control groups using computer-generated random numbers, which were assigned to an anonymized list of participants. The principal investigator (KS) passed the randomization schedule on to the practice nurses shortly before the appointment for delivering the intervention.” (pg 146)
Selective reporting (reporting bias)	Unclear risk	No protocol available; although it appears that everything was reported it is difficult to determine this without a protocol
Other bias	High risk	“There is also a possibility that MEMS® may have altered patient behaviour, although it is unlikely that this effect would have persisted throughout the whole study period.” “We do not know if the high adherence levels observed in this RCT were due to a self selected population, orwhether the results reflect generally higher adherence levels in the UK.” (pg 150) “Baseline blood pressures in both groups were close to our chosen cut-off point of $\geq 150/90$ , and only 94 out of 245 participants (39%) were ‘uncontrolled’.” “Lastly, with this study design there was potential for contamination.” (pg 149)
Blinding of outcome assessment (detection bias) Adherence measure	Low risk	(PRIMARY)MEMS -OpenRCT; practice nurses were aware of the group allocation. However, low risk proposed because it appears that practice nurses were not involved in data collection and unaware of results until completion of the study
Blinding of outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE

assessment (detection bias) Patient outcome		MEASUREMENT - No information on whether the method of taking blood pressure was automated. There is insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of participants (performance bias) Adherence measure	High risk	(PRIMARY)MEMS -No patient blinding. "In this open RCT both the study participants and the practice nurses were aware of the group assignment at completion of the Interventions for baseline period". (pg 146)
Blinding of participants (performance bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT - There is insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of personnel (performance bias) Adherence outcome	Unclear risk	(PRIMARY) MEMS - No information on blinding given. There is insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of personnel (performance bias) Patient measure	Unclear risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT - No information on blinding given. There is insufficient information to permit judgment of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk	(PRIMARY) MEMS - 85% follow-up in intervention group; 80.3% in the control. Actual sample size (245) is less than power calculations (330). No significant difference in outcome between groups
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk	(PRIMARY) BLOOD PRESSURE MEASUREMENT - Dropouts not equal across groups and reasons not given for all dropouts

<b>Stewart 2014</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	Sealed opaque envelope but not reported if they were sequentially numbered.
Allocation concealment (selection bias)	Unclear risk of bias	'sealed envelope technique' used but insufficient information provided to justify "low risk" assessment.
Selective reporting (reporting bias)	High risk of bias	Protocol states that they will measure patient adherence and persistence at the end of six months, changes in patients'

		BP control, satisfaction with and willingness to pay for the service and economic benefits. Satisfaction with and willingness to pay for the service and economic benefits are not reported on.
Other bias	Low risk of bias	To check for any 'Hawthorne effect' [20, 21] in the UCG due to the effect of data collection, a third group of patients (Hidden Control Group - HCG) who are taking or have taken antihypertensives in the previous six months (but not included as participants in the UCG) will also be identified.
Blinding of outcome assessment (detection bias) Adherence measure	High risk of bias	SELF-REPORT - MORISKY No blinding of outcome assessment, and outcome could have been affected
Blinding of outcome assessment (detection bias) Adherence measure	High risk of bias	SELF-REPORT - TABS No blinding of outcome assessment, and outcome could have been affected
Blinding of outcome assessment (detection bias) Patient outcome	High risk of bias	CHANGE IN BP CONTROL Pharmacists measured the outcomes and they were not blinded to study group.
Blinding of participants (performance bias) Adherence measure	High risk of bias	SELF-REPORT - MORISKY Pharmacists gathered the outcome data and knew which study group the patient was in
Blinding of participants (performance bias) Adherence measure	High risk of bias	SELF-REPORT - TABS Pharmacists gathered the outcome data and knew which study group the patient was in
Blinding of participants (performance bias) Patient outcome	Low risk of bias	CHANGE IN BP CONTROL No blinding, but outcome unlikely to be affected by patient blinding.
Blinding of personnel (performance bias) Adherence outcome	High risk of bias	SELF-REPORT - MORISKY Subjective measure. No blinding, and outcome is likely to be affected.
Blinding of personnel (performance bias) Adherence outcome	High risk of bias	SELF-REPORT - TABS Subjective measure. No blinding, and outcome is likely to be affected.
Blinding of personnel (performance bias) Patient measure	Low risk of bias	CHANGE IN BP CONTROL Objective measure. Outcome unlikely to be affected by blinding.
Incomplete outcome	Unclear risk of bias	SELF-REPORT - MORISKY

data (attrition bias) Adherence measure		One pharmacy pulled out due to change in ownership. Study provided reasons for loss but did not actively address.
Incomplete outcome data (attrition bias) Adherence measure	Unclear risk of bias	SELF-REPORT - TABS One pharmacy pulled out due to change in ownership. Study provided reasons for loss but did not actively address.
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk of bias	CHANGE IN BP CONTROL Insufficient information to make judgement.

<b>Svarstad 2013</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	The study statistician used computer software to randomize the 28 sites into an intervention group (TEAM Care or TC) and a control group (Usual Care or UC).
Allocation concealment (selection bias)	Low risk of bias	All screenings were conducted by project assistants, who were hired and supervised by investigators, blinded to pharmacy allocation, and trained to obtain consents and three blood pressure readings with 30-second intervals between readings. Primary and secondary outcomes were assessed 6 and 12 months after enrollment using blinded data collectors, prescription profiles, and program records.
Selective reporting (reporting bias)	High risk of bias	Cost-effectiveness analysis is mentioned in the protocol paper but not in this paper.
Other bias	Low risk of bias	Some patients may have obtained medications from other sources after enrollment, though bias is unlikely because we did not find between-group differences in the use of hospitals, clinics, or other pharmacies after enrollment.
Blinding of outcome assessment (detection bias)	Low risk of bias	PHARMACY REFILL RECORDS Investigators blinded to study allocation.

Adherence measure		
Blinding of outcome assessment (detection bias) Patient outcome	Low risk of bias	<b>BLOOD PRESSURE CHANGE</b> The University of Wisconsin Survey Center (UWSC) was contracted by the study director (B.L.S.) to relocate all patients and perform the 6- and 12-month interviews according to protocol. UWSC is nationally recognized for state-of-the-art methods of tracking, relocating, and interviewing participants in longitudinal studies (www.uwsc.wisc.edu). UWSC interviewers were blinded to pharmacy allocation, were not involved in recruitment or intervention, and were trained by an investigator (J.M.K.) to obtain three blood pressure readings using the same monitor and AHA guidelines used at baseline. The second and third readings were averaged and used in analyses.
Blinding of participants (performance bias) Adherence measure	Unclear risk of bias	<b>PHARMACY REFILL RECORDS</b> Insufficient information provided.
Blinding of participants (performance bias) Patient outcome	Low risk of bias	<b>BLOOD PRESSURE CHANGE</b> The University of Wisconsin Survey Center (UWSC) was contracted by the study director (B.L.S.) to relocate all patients and perform the 6- and 12-month interviews according to protocol. UWSC is nationally recognized for state-of-the-art methods of tracking, relocating, and interviewing participants in longitudinal studies (www.uwsc.wisc.edu). UWSC interviewers were blinded to pharmacy allocation, were not involved in recruitment or intervention, and were trained by an investigator (J.M.K.) to obtain three blood pressure readings using the same monitor and AHA guidelines used at baseline. The second and third readings were averaged and used in analyses.
Blinding of personnel (performance bias) Adherence outcome	High risk of bias	<b>PHARMACY REFILL RECORDS</b> Pharmacy allocation was concealed from patients until investigators verified that enrollment goals were met at their pharmacy.
Blinding of personnel	Low risk of bias	<b>BLOOD PRESSURE CHANGE</b>

(performance bias) Patient measure		Pharmacy allocation was concealed from patients until investigators verified that enrollment goals were met at their pharmacy. Objective measure from patient's point of view.
Incomplete outcome data (attrition bias) Adherence measure	Low risk of bias	PHARMACY REFILL RECORDS Missing data balanced across groups, similar reasons for missing data across groups.
Incomplete outcome data (attrition bias) Patient outcome	Low risk of bias	PHARMACY REFILL RECORDS Missing data balanced across groups, similar reasons for missing data across groups.

<b>Tinsel 2013</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	They randomly selected GP practices (including their patients) for the intervention or control group, respectively. The randomisation was conducted by staff members of the Division of General Practice, University Medical Centre Freiburg. No stratification was used. Not enough information provided
Allocation concealment (selection bias)	Low risk of bias	GP practices were randomly allocated, and patients were blinded to the allocation of the intervention.
Selective reporting (reporting bias)	Low risk of bias	All outcomes specified in the protocol were reported on.
Other bias	High risk of bias	Because most of the participating GPs were academic family doctors associated with the Division of General Practice of the University Medical Centre Freiburg (Germany), the external validity of our results seems to be limited. Therefore we may assume that the participating GPs are probably more open-minded as to taking part in studies and improving their skills when compared to all GPs in the region. Thus, e.g., we assume that GPs who were interested in improving

		their antihypertensive treatment or their communication skills were overrepresented in this study The internal validity of the study is limited to some extent because the intervention itself could not be blinded for the GPs.
Blinding of outcome assessment (detection bias) Adherence measure	High risk of bias	SELF-REPORT - QUESTIONNAIRE Self report In each of the four data collections, questionnaires were distributed to the patients by their GP practices.
Blinding of outcome assessment (detection bias) Patient outcome	Low risk of bias	BLOOD PRESSURE Objective measure. Outcome unlikely to be affected by blinding.
Blinding of outcome assessment (detection bias) Patient outcome	Low risk of bias	CARDIOVASCULAR RISK SCORE Objective measure. Outcome unlikely to be affected by blinding.
Blinding of participants (performance bias) Adherence measure	High risk of bias	SELF-REPORT - QUESTIONNAIRE GPs were not blinded Not enough information provided on other study personnel.
Blinding of participants (performance bias) Patient outcome	Low risk of bias	BLOOD PRESSURE Objective measure. Outcome unlikely to be affected by blinding.
Blinding of participants (performance bias) Patient outcome	Low risk of bias	CARDIOVASCULAR RISK SCORE Objective measure. Outcome unlikely to be affected by blinding.
Blinding of personnel (performance bias) Adherence outcome	High risk of bias	SELF-REPORT - QUESTIONNAIRE Subjective measure even though participants were blinded to study group.
Blinding of personnel (performance bias) Patient measure	Low risk of bias	BLOOD PRESSURE Objective measure. Participants were blinded to study group.
Blinding of personnel (performance bias) Patient measure	Low risk of bias	CARDIOVASCULAR RISK SCORE Objective measure. Outcome unlikely to be affected by blinding.
Incomplete outcome data (attrition bias) Adherence measure	Low risk of bias	SELF-REPORT - QUESTIONNAIRE Missing data imputed using appropriate methods.
Incomplete outcome	Unclear risk of bias	BLOOD PRESSURE

data (attrition bias) Patient outcome		Not enough information reported.
Incomplete outcome data (attrition bias) Patient outcome	Unclear risk of bias	CARDIOVASCULAR RISK SCORE Insufficient information.

<b>Wong 2013</b>	<b>Risk of bias</b>	
Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	The attending physician received a random number generated by the computer which assigned the participant in one of the two groups in a pre-determined 1:1.5 allocation ratio (intervention vs. control).
Allocation concealment (selection bias)	Unclear risk of bias	Concealment not described in enough detail to make accurate judgement
Selective reporting (reporting bias)	Unclear risk of bias	No protocol available
Other bias	Low risk of bias	None reported
Blinding of outcome assessment (detection bias) Adherence measure	Low risk of bias	SELF-REPORT - QUESTIONNAIRE To avoid inter-group contamination, each patient was assessed on their drug adherence and blood pressure levels by the same research assistant 3- and 6-months after the initial clinic visit. Two 3-monthly visits were arranged for each participant. The researchers who conduct these measurements were blinded to the group allocated
Blinding of outcome assessment (detection bias) Patient outcome	Low risk of bias	BP CHANGE The researchers who conduct these measurements were blinded to the group allocated
Blinding of participants (performance bias) Adherence measure	Unclear risk of bias	SELF-REPORT - QUESTIONNAIRE Insufficient information to make a judgement.
Blinding of participants (performance bias) Patient outcome	Unclear risk of bias	BP CHANGE Insufficient information to make a judgement.
Blinding of personnel (performance bias)	High risk of bias	SELF-REPORT - QUESTIONNAIRE Subjective measure.

Adherence outcome		
Blinding of personnel (performance bias) Patient measure	Low risk of bias	BP CHANGE Objective measure.
Incomplete outcome data (attrition bias) Adherence measure	Low risk of bias	SELF-REPORT - QUESTIONNAIRE Attrition and exclusions reported, missing data balanced in numbers across groups, reasons for missing data unlikely to be related to true outcome
Incomplete outcome data (attrition bias) Patient outcome	Low risk of bias	BP CHANGE Drop out balanced between groups. reasons for drop out similar between groups.

## Appendix VII: GP information sheet



### Participant Information Sheet

#### General Practitioners Views of Medication Adherence Apps for Hypertension

##### *Overview*

You are being invited to take part in a study exploring non adherence to antihypertensive medications and the potential use of smartphones as an adherence aid.

Before you decide, it is important that you understand why the research is being done and what it will involve. If there is anything you are not clear about, we will be happy to explain it to you. Please take as much time as you need to read this information. You should only consent to participate in this research study when you feel you understand what is being asked of you, and you have had enough time to think about your decision.

##### *Who is doing the research?*

The research is being conducted by Eimear Morrissey, a PhD Candidate from the School of Psychology at the National University of Ireland, Galway. The research team also includes Dr. Gerry Molloy and Dr. Jane Walsh; lecturers in the School of Psychology in NUI, Galway and Liam Glynn, General Practitioner and senior lecturer in the School of Medicine in NUI, Galway.

##### *What is the research about?*

Lots of people report difficulties in taking their blood pressure medication consistently and on time. This research is investigating GP's thoughts and opinions about using a smartphone app to help them with this.

##### *What you will be asked to do*

You will take part in a semi-structured interview with the lead researcher. You will be invited to discuss adherence to anti-hypertensive medications and your thoughts and views around the use of technology as an adherence aid. Each interview is scheduled to last approximately 15 minutes. Everything discussed will be kept completely confidential.

In order to accurately capture the group discussions, the researcher will record audio of the session. Selective quotes may be used to illustrate points in any resulting publications. However these quotes will be completely anonymous.

#### *What's next?*

It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to keep this *Information Sheet* and to read a *Consent Form*. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your rights in any way. Although we hope you will join us, participation is voluntary.

#### *Contact*

If you have any queries about the project, you can contact the lead researcher –

Eimear Morrissey – [e.morrissey6@nuigalway.ie](mailto:e.morrissey6@nuigalway.ie)

Alternatively the following people can also be contacted –

Dr. Gerry Molloy – [gerry.molloy@nuigalway.ie](mailto:gerry.molloy@nuigalway.ie)

Dr. Jane Walsh – [jane.walsh@nuigalway.ie](mailto:jane.walsh@nuigalway.ie)

Dr. Liam Glynn – [liam.glynn@nuigalway.ie](mailto:liam.glynn@nuigalway.ie)

If you have any concerns about this study and wish to contact someone in confidence, you may contact Dr. AnnMarie Groarke, Head of the School of Psychology, National University of Ireland, Galway (091-4953098 or [annmarie.groarke@nuigalway.ie](mailto:annmarie.groarke@nuigalway.ie))

## Appendix VIII: GP consent form



### Participant Consent Form

#### General Practitioners Views of Medication Adherence Apps for Hypertension

##### Queries

If you have any questions regarding this consent form or any other questions about this study, please contact Eimear Morrissey ([e.morrissey6@nuigalway.ie](mailto:e.morrissey6@nuigalway.ie)) or one of her supervisors:

- Dr. Gerry Molloy ([gerry.molloy@nuigalway.ie](mailto:gerry.molloy@nuigalway.ie))
- Dr. Jane Walsh ([jane.walsh@nuigalway.ie](mailto:jane.walsh@nuigalway.ie))

If Ms. Morrissey or her supervisors are unable to address your concerns satisfactorily, please contact the Head of the School of Psychology, National University of Ireland, Galway.

#### **PARTICIPATION IS STRICTLY VOLUNTARY.**

#### **Please initial EACH box and sign your name in the space below**

1. I confirm that I have read the document entitled 'Participant Information Sheet' and have had the opportunity to ask questions.
2. I am satisfied that I understand the information provided and have had enough time to consider the information.
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected.
4. I agree to take part in the above study.

Name: \_\_\_\_\_ (Please use block capitals)

Signature: \_\_\_\_\_

Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

## Appendix IX: GP topic guide

<b>Intro</b>		Prompts
	Tell me a bit about the hypertensive patients you typically see here	Age range  Sex  Type of hypertension – newly diagnosed/resistant etc
<b>Usual Care</b>	When you see a hypertensive person for the first time, what happens?	What do you talk about?  How do you think that information is usually received?  What issues does the person usually raise?
	When would typically prescribe anti-hypertensive medication?	Certain BP values  Other lifestyle interventions – exercise, diet, salt  Amount of antihypertensive medications  What percentage of all hypertensive patients are prescribed medication?
	What have you found to be the main impediments in initiating treatment in hypertension?	Patient reluctance  Are there any specific patient groups in which you find it difficult to initiate anti-hypertensives?
	Do you discuss the adherence issues specifically?	Tell me about that...  - Need for adherence for the medication to work  - Would you feel that some people need more adherence advice than other? How would you judge this?  - Do you know what advice to give?
	Having the conversation	How do you feel talking about adherence?  How is it received? (defensive, agreeable)  How could this conversation be made easier? (for you/the patient)

	How are these issues followed up?	If it is obvious that a patient is not adhering to their medication, what would you do?
<b>Behaviour Change</b>	Can you think of times where patients have made positive life style changes as a result of having hypertension? – particularly in terms of medication use	Tell me about that...  Motivations, Supports, Outcome
	And those who haven't made any changes, what were the barriers?	Any targeted support available?
	Have you seen technology being used to support adherence?	<ul style="list-style-type: none"> <li>- What kind, features,</li> <li>- Did someone recommend it?</li> <li>- What information was it providing to the patient?</li> </ul>
	How about other kinds of technology?	<p>What about mobile phone apps, text message/phone, web based information forums, pedometer, remote monitoring?</p> <p>Would these support mechanisms be useful?</p> <p>If it provided you with information as well – helpful data vs duty of care</p>
As a GP, would you consider or feel comfortable with prescribing technology, such as a smartphone app, to a hypertensive patient? If yes – why? If no – why?	<ul style="list-style-type: none"> <li>- Content of app</li> <li>- Adherence app in general vs. a specific app</li> <li>- HSE approval? (Like NHS app library)</li> <li>- Evidence of effectiveness (like evidence of effectiveness in a drug)</li> <li>- Demographics of the population (hypertensive patients tend to be &gt;55 years)</li> <li>- Would you be more likely to recommend an app to some people more so than others? How would you judge this?</li> </ul>	
Do you have the same opinion for other conditions or behaviours?	<ul style="list-style-type: none"> <li>- For example, adherence in Type I diabetic patients/asthmatics</li> <li>- Other behaviour change e.g. PA for obese patient</li> </ul>	

	Any other comments or suggestions on how technology could or could not support adherence behaviour change?	
--	--	--

## Appendix X: Recruitment material



Are you taking blood pressure medication?

Would you like a €20 one for all voucher?

Researchers at NUI Galway with the support of Croí, are currently inviting adults who have been prescribed at least one form of blood pressure medication, to participate in a study involving the use of a smartphone app to help with medication taking.

Participants will be invited to take part in a group discussion. The group discussion will be around taking medication, and looking at a smartphone app that has been designed to help people to take their medication. Participant views and personal experiences are extremely valuable and their input will greatly help the researcher in the development of an intervention for individuals with high blood pressure who struggle with medication taking.

The discussion groups are part of a PhD research project being carried out at NUI Galway by student Eimear Morrissey with Dr Gerry Molloy and Dr. Jane Walsh of the University's School of Psychology. The study is supported by Irish Research Council.

The discussion groups will be made up of 3-4 people who have volunteered to participate, and will be led by Ms. Morrissey. Refreshments will be provided to participants and each session is scheduled to last approximately 1 hour. The discussion groups will be held at Croí. All participants will receive a €20 one-for-all voucher for their participation.

The discussion groups will take place on the week of the 7<sup>th</sup> to the 11<sup>th</sup> of November. If you are interested, or would like further information, please contact Eimear by Friday the 22<sup>nd</sup> October -

0876708518 / [e.morrissey6@nuigalway.ie](mailto:e.morrissey6@nuigalway.ie)

Eimear Morrissey, School of Psychology, Arts Millennium Building Extension, NUI, Galway.

## Appendix XI: Participant information sheet



### Participant Information Sheet

#### Can smartphone apps help with taking your blood pressure medication?

##### *Overview*

You are being invited to take part in a study exploring the use of smartphone apps to help take blood pressure medication.

Before you decide, it is important that you understand why the research is being done and what it will involve. If there is anything you are not clear about, we will be happy to explain it to you. Please take as much time as you need to read this information. You should only consent to participate in this research study when you feel you understand what is being asked of you, and you have had enough time to think about your decision.

##### *Who is doing the research?*

The research is being conducted by Eimear Morrissey, a PhD Candidate from the School of Psychology at the National University of Ireland, Galway. The research team also includes Dr. Gerry Molloy and Dr. Jane Walsh; lecturers in the School of Psychology in NUI, Galway and Liam Glynn, General Practitioner and senior lecturer in the School of Medicine in NUI, Galway.

##### *What is the research about?*

Lots of people report difficulties in taking their blood pressure medication consistently and on time. This research is investigating people's thoughts and opinions about using a smartphone app to help them with this.

##### *What you will be asked to do*

**You will be invited to take part in a group discussion.** The group will consist of you, the researcher and four other participants. You will have an opportunity to discuss your experiences of hypertension and taking blood pressure medication. The researcher will then show you an app. You will be given an opportunity to use the app and then there will be a discussion. You can talk about using the app e.g. what you liked and disliked about it and what features you found helpful. You will also be able to make suggestions on how to improve the app. It will be a casual environment and refreshments will be provided. Each session is scheduled to last approximately one hour. Everything discussed will be kept completely confidential.

##### *Your data*

In order to accurately capture the group discussions, the researcher will record audio of the session. Selective quotes may be used to illustrate points in any resulting publications. However these quotes will be completely anonymous.

The study is being supported by two smartphone apps – PatientMPower and MiBP. It is possible that these companies may use any data collected to inform future design of their products.

#### *What's next?*

It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to keep this *Information Sheet* and to read a *Consent Form*. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your rights in any way. Although we hope you will join us, participation is voluntary.

#### *Contact*

If you have any queries about the project, you can contact the lead researcher –

Eimear Morrissey – [e.morrissey6@nuigalway.ie](mailto:e.morrissey6@nuigalway.ie)

Alternatively the following people can also be contacted –

Dr. Gerry Molloy – [gerry.molloy@nuigalway.ie](mailto:gerry.molloy@nuigalway.ie)

Dr. Jane Walsh – [jane.walsh@nuigalway.ie](mailto:jane.walsh@nuigalway.ie)

Dr. Liam Glynn – [liam.glynn@nuigalway.ie](mailto:liam.glynn@nuigalway.ie)

If you have any concerns about this study and wish to contact someone in confidence, you may contact Dr. AnnMarie Groarke, Head of the School of Psychology, National University of Ireland, Galway (091-4953098 or [annmarie.groarke@nuigalway.ie](mailto:annmarie.groarke@nuigalway.ie))

## Appendix XII: Participant consent form



### High Blood Pressure: Apps for Medication Adherence

#### Participant Consent Form

#### Can smartphone apps help with taking your blood pressure medication?

#### Queries

If you have any questions regarding this consent form or any other questions about this study, please contact Eimear Morrissey ([e.morrissey6@nuigalway.ie](mailto:e.morrissey6@nuigalway.ie)) or one of her supervisors:

- Dr. Gerry Molloy ([gerry.molloy@nuigalway.ie](mailto:gerry.molloy@nuigalway.ie))
- Dr. Jane Walsh ([jane.walsh@nuigalway.ie](mailto:jane.walsh@nuigalway.ie))

If Ms. Morrissey or her supervisors are unable to address your concerns satisfactorily, please contact the Head of the School of Psychology, National University of Ireland, Galway.

#### **PARTICIPATION IS STRICTLY VOLUNTARY.**

#### **Please initial EACH box and sign your name in the space below**

5. I confirm that I have read the document entitled 'Participant Information Sheet' and have had the opportunity to ask questions.
6. I am satisfied that I understand the information provided and have had enough time to consider the information.
7. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected.
8. I agree to take part in the above study.

Name: \_\_\_\_\_ (Please use block capitals)

Signature: \_\_\_\_\_

Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

### Appendix XIII: Focus group topic guide

	Prompts
<b>Introduction</b>	
Introduction	Names and places
Hypertension diagnosis	<p>I don't know much about the experience of having high blood pressure – tell me about it. What does it mean for you?</p> <p>When was your high blood pressure diagnosed? How did you react the diagnosis?</p> <p>Did you get high blood pressure related information? If so, where?</p> <p>How do you manage it? – PA/diet/medication</p> <p>Tell me more about the medication – what do the medications do? How do you feel about taking them?</p> <p>Have you experienced side effects? Tell me more about that – are they manageable/disruptive?</p> <p>How many medications are you taking?</p>
Medication taking	<p>Do you take your blood pressure medication as prescribed?</p> <p>What barriers do you come across to taking your medications? – forgetfulness/change in routine/financial cost/side effects</p> <p>Does this cause any stress?</p> <p>What helps you to remember to take your medication correctly? – reminders/habit creation/social support - spouse</p>
Technology	<p>Do you use technology such as mobile phones, the internet, apps in your every day life?</p> <p>Do you use any of these kinds of technology for health? E.g. pedometer/fitness tracker/diet tracker</p>

	<p>Have you ever use these kinds of technology to help manage your hypertension?</p> <p>If not, why?</p> <p>If so, would you find it difficult without it?</p>
<b>Think aloud</b>	
<p>Patients are given app and BP monitor. Think aloud methodology is used</p>	<p>Patients are asked to phrase their thoughts aloud as they navigate the app and monitor</p> <p><i>What are your first impressions of this app?</i></p> <p><i>What are you thinking now?</i></p> <p><i>What made you choose that option?</i></p> <p><i>What do you think about [this activity, this information, function]?</i></p> <p><i>Can you tell me a bit more about why you think that?</i></p> <p><i>What is it you like about that?</i></p> <p><i>That's really interesting.....</i></p> <p><i>Mmmmm</i></p> <p><b>Systems usability scale?</b></p>
<b>Post think aloud</b>	
<p>General usability questions</p>	<p>Can you tell me about your first thoughts when you saw the app?</p> <p>How did you find the app overall?</p> <p>What did you like about the app? – content/appearance</p> <p>What did you dislike about the app?</p> <p>What could be improved in this app?</p> <p>Is there anything that surprised you?</p> <p>What was your general experience of using this app?</p> <p>Have you come across apps like this before?</p>

	<p>If so, how does this one compare?</p> <p>Does it help to have used health apps before? Or was it clear enough?</p>
<p>Potential feasibility</p>	<p>Would you use an app and BP monitor like this in your everyday life to manage your hypertension?</p> <ul style="list-style-type: none"> <li>- Why/why not</li> <li>- What exactly would be stopping you</li> <li>- What would make it easier</li> </ul> <p>Are there any features of the app and monitor that you found particularly useful?</p> <p>Are there any aspects that you definitely would not be interested in?</p> <p>Would this app have made any difference if you had access to it ten years ago?</p> <p>How do you think it could affect your blood pressure in the future?</p>
<p>Any further issues</p>	

## Appendix XIV: COREQ checklist

Item	Description
<b>Domain 1: Research team and reflexivity</b>	
<i>Personal Characteristics</i>	
1. Interviewer/facilitator	One author (EM) conducted the focus groups
2. Credentials	BA., MSc.
3. Occupation	PhD Candidate
4. Gender	Female
5. Experience and training	Trained in qualitative methods and design, experience in conducting focus groups
<i>Relationship with participants</i>	
6. Relationship established	Potential participants contacted EM via email or telephone to discuss arrangements for the focus groups. Otherwise participants had no relationship with the researcher.
7. Participant knowledge of the interviewer	Participants were informed that the researcher was conducting a PhD in the area of digital interventions for hypertension and her goal was to understand hypertensive patients' perspectives on this.
8. Interviewer characteristics	The researcher was closely engaged in the research process and therefore unable to avoid personal bias. This research sought to inform the content of an intervention.
<b>Domain 2: study design</b>	
<i>Theoretical framework</i>	
9. Methodological orientation and theory	Thematic analysis was used in this study. An inductive approach was adopted

### *Participant selection*

- |                        |  |
|------------------------|--|
| 10. Sampling           | Patients with hypertension in the west of Ireland were sampled purposively.  |
| 11. Method of approach | From October to November 2016, Croí (a cardiac health charity) advertised the study through email and social media channels. |
| 12. Sample size        | There were 24 participants in the study.   |
| 13. Non-participation  | All participants who agreed on a date and a time took part in a focus group  |

### *Setting*

- |                                  |  |
|----------------------------------|--|
| 14. Setting of data collection   | Data was collected at Croi House, the charities dedicated heart and stroke centre. |
| 15. Presence of non-participants | No non-participants were present.  |
| 16. Description of sample        | Characteristics of the sample can be seen in Table 1.                              |

### *Data collection*

- |                            |  |
|----------------------------|--|
| 17. Interview guide        | The focus group schedule was developed by reviewing other qualitative research in the area. It was then reviewed by the research team and piloted on two patients with hypertension.   |
| 18. Repeat interviews      | No repeat interviews were carried out.   |
| 19. Audio/visual recording | Audio recording was used to collect the data.  |
| 20. Field notes            | Field notes were made during and after the focus groups.   |
| 21. Duration               | Each of the focus groups lasted approximately one hour.  |
| 22. Data saturation        | The researchers decided that data saturation had been achieved after the 8 <sup>th</sup> focus group. The transcripts were reviewed as soon as possible after each focus group. Saturation was achieved as no further additional new information began to emerge. It was agreed that the addition of new codes was unlikely after 8 <sup>th</sup> focus group. |

23. Transcripts returned Transcripts were not returned to participants for comment and/or correction.

### **Domain 3: analysis and findings**

#### *Data analysis*

24. Number of data coders Two data coders (EM and MC) coded the data

25. Description of the coding tree Open coding was firstly performed. This consisted of transcripts being read thoroughly and sections of text being assigned to descriptive codes. Content of the transcripts was constantly compared to codes that were already established. After forming the codes, they were grouped into categories, which were then grouped into themes.

26. Derivation of themes All five members of the research team came together to review all the data and contribute to the thematic analysis.

27. Software Data was managed using NVivo 11.

28. Participant checking Participants did not provide feedback on the findings.

#### *Reporting*

29. Quotations presented Participant quotations are presented to illustrate the themes/findings. Each quotation is identified using the participants' age and gender.

30. Data and findings consistent There is consistency between the data presented and the findings. The unit of analyses was the theme rather than the prevalence or frequency of statements. Some statements of quantification are included (e.g., statements such as often, sometimes), but do not always aim to provide estimates of prevalence.

31. Clarity of major themes Codes identified in the open coding stage were discussed by two study authors until consensus was reached. All major themes clearly presented in the findings.

32. Clarity of minor themes No minor themes were present

