Université de Montréal

Compliance measurement-guided medication management programs in hypertension:
a systematic review

par
Sergey Golubev

Administration de la santé
Faculté de médecine

Mémoire présenté à la Faculté des études supérieures
en vue de l'obtention du grade de Maîtrise ès sciences
en Évaluation des technologies de la santé

Décembre, 2010

Université de Montréal
Faculté des études supérieures et postdoctorales

Ce mémoire intitulé :

Compliance measurement-guided medication management programs in hypertension : a systematic review

Présenté par :
Sergey Golubev

a été évalué par un jury composé des personnes suivantes :

.....
Sicotte Claude, Président-rapporteur
Johri Mira, Directrice de recherche
Lamothe Lise, Membre du jury

Résumé

Objectif principal Il n'est pas démontré que les interventions visant à maîtriser voire modérer la médicamentation de patients atteints d'hypertension peuvent améliorer leur gestion de la maladie. Cette revue systématique propose d'évaluer les programmes de gestion contrôlée de la médicamentation pour l'hypertension, en s'appuyant sur la mesure de l'observance des traitements par les patients (CMGM).

Design Revue systématique.

Sources de données MEDLINE, EMBASE, CENTRAL, résumés de conférences internationales sur l'hypertension et bibliographies des articles pertinents.

Méthodes Des essais contrôlés randomisés (ECR) et des études observationnelles (EO) ont été évalués par 2 réviseurs indépendants. L'évaluation de la qualité (de ce matériel) a été réalisée avec l'aide de l'outil de Cochrane de mesure du risque de biais, et a été estimée selon une échelle à quatre niveaux de qualité Une synthèse narrative des données a été effectuée en raison de l'hétérogénéité importante des études.

Résultats 13 études (8 ECR, 5 EO) de 2150 patients hypertendus ont été prises en compte. Parmi elles, 5 études de CMGM avec l'utilisation de dispositifs électroniques comme seule intervention ont relevé une diminution de la tension artérielle (TA), qui pourrait cependant être expliquée par les biais de mesure. L'amélioration à court terme de la TA sous CMGM dans les interventions complexes a été révélée dans 4 études à qualité faible ou modérée. Dans 4 autres études sur les soins intégrés de qualité supérieure, il n'a pas été possible de distinguer l'impact de la composante CMGM, celle-ci pouvant être compromise par des traitements médicamenteux. L'ensemble des études semble par ailleurs montrer qu'un feed-back régulier au médecin traitant peut être un élément essentiel d'efficacité des traitements CMGM, et peut être facilement assuré par une infirmière ou un pharmacien, grâce à des outils de communication appropriés.

Conclusions Aucune preuve convaincante de l'efficacité des traitements CMGM comme technologie de la santé n'a été établie en raison de designs non-optimaux des études identifiées et des ualités méthodologiques insatisfaisantes de celles-ci. Les recherches futures devraient : suivre les normes de qualité approuvées et les recommandations cliniques actuelles pour le traitement de l'hypertension, inclure des groupes spécifiques de patients avec des problèmes d'attachement aux traitements, et considérer les résultats cliniques et économiques de l'organisation de soins ainsi que les observations rapportées par les patients.

Mots-clés : hypertension, des médicaments antihypertensifs, attachement des patients au traitement medicamentif, surveillance électronique, nombre de comprimés, revue systématique, évaluation des technologies de la santé, évaluation des soins intégrés

Abstract

Objective Whether interventions including measurement and correction of patients' attitude to antihypertensive medication can improve hypertension management is unclear. The review aims to determine the effectiveness of patient compliance measurement-guided medication management (CMGM) programs in essential hypertension.

Design Systematic review.

Data sources MEDLINE, EMBASE, CENTRAL, hypertension meetings abstracts, and bibliographies of identified articles.

Methods Randomized controlled trials (RCT) and observational studies (OS) were assessed by 2 reviewers independently. Quality assessment was performed with the Cochrane risk of bias tool and evaluated in a four-point continuum. A narrative data synthesis was performed due to significant heterogeneity among studies.

Results 13 studies (8 RCT, 5 OS) involving 2150 hypertensives were included. Five trials of CMGM with electronic devices as a sole intervention suggested decrease in blood pressure (BP) but the result may have been due to bias. Short-term BP improvement under CMGM in complex interventions was revealed in 4 studies of low-to-moderate quality. In 4 integrated care studies of higher quality the impact of CMGM component was not possible to distil and may be compromised by medication regimens. Regular feedback to the treating physician seems to be an essential component of CMGM and may be effectively mediated by a nurse or a pharmacist and via telecommunication.

Conclusions No convincing evidence for the effectiveness of CMGM as a health technology was found due to non-optimal study designs and methodological quality. Future research should follow accepted quality standards and current guidelines for the treatment of hypertension, include specific groups of patients with compliance problems and consider clinical, economic, patient-reported and organizational outcomes.

Keywords: Hypertension, antihypertensive medication, patient compliance, patient adherence, medication adherence, electronic monitoring, pill count, systematic review, health technology assessment, integrated care

List of contents

List of tables

List of figures

List of abbreviations

ABPM - ambulatory blood pressure monitoring

ACEI – angiotensin-converting enzyme inhibitor

BP – blood pressure

C – compliance (in tables)

CG – control group

CHERG – Child Health Epidemiology Reference Group

CMGM – compliance measurement-guided management

DBP – diastolic blood pressure

ECMD – electronic compliance monitoring device

IF – Inna Fedoseyeva

IG – intervention group

NS – not significant (in tables)

NSp – not specified (in tables)

OS – observational study

PICOS – population – intervention - comparators – outcomes – study design

PRISMA – Preferred Reporting Items for Systematic reviews and Meta-Analyses

RCT – randomized controlled trial

SBP – systolic blood pressure

SD – standard deviation

SEM – standard error of mean

SG – Sergey Golubev

UC – usual care

In memoriam of my sister Anne,
who died in 2008
due to imperfection of
medical technologies

Acknowledgements

I would like to thank my exceptional mentor and advisor throughout the entire period of my studies, Prof. Mira Johri. I want to thank her especially for offering invaluable guidance, helping me develop my project, providing detailed comments and suggestions on this work, for her solid thoughtful advice and kind support on my long and sometimes problematic way in the novel world of health technology assessment.

I express my sincere gratitude to all students, teachers and staff of the unique ULYSSES Program, International Master's Program in Health Technology Assessment & Management, 4th edition for fruitful communications and the joy of learning.

I appreciate the kind well-timed help of Prof. Albert Wertheimer (Temple University, Philadelphia) and Dr. Pavel Crystal (Mont Sinai Hospital, Toronto) in breaking information barriers between countries and institutions.

Contributions of authors

Sergey Golubev (SG), MD, PhD (Cardiology) was the main author of the review, designed the research question, drown up the protocol, created search strategies; undertook study selection, the data extraction and analysis, quality assessment, and performed the preparation of the manuscript.

Inna Fedoseyeva (IF), MD, PhD (Clinical Pharmacology) undertook study selection, the data extraction, quality assessment and was involved in reviewing differences of opinion and consensus making in association with SG.

This manuscript has not been previously published. The review protocol and preliminary results were presented at the 20th European Meeting on Hypertension held in Oslo, Norway, June 18-21, 2010.

Introduction

Patients' non-compliance with prescribed medication regimens is common worldwide and poses a significant clinical practice problem.[1] It can influence effectiveness, safety and cost-effectiveness of therapeutic interventions via deterioration of patients' health outcomes, the need for additional consultations and other services, the use of extra drugs, avoidable hospital admissions and increases in direct and indirect costs of management.[2,3] A recent meta-analysis revealed that the risk of mortality for those who were compliant with drug therapy was about half that of participants who were not.[4]

High blood pressure (BP) or essential hypertension is the most prevalent cardiovascular disorder worldwide, and simultaneously a major risk factor for cardiovascular morbidity and mortality with their important socioeconomic burden. [5] Evidence from randomized controlled trials (RCT) has clearly shown that effective drug treatment of hypertension reduces the risk of cardiovascular morbidity and mortality, mainly through improved BP control.[6] Nevertheless, there is ongoing concern that the benefits demonstrated in RCTs of antihypertensive drug treatment are not realized in everyday clinical practice.[7,8] BP control is still far from optimal worldwide, and non-compliance has been suggested as a major reason for treatment failure. [9,10,11]

Although the gold standard in patient compliance evaluation is not yet established, an important progress in concepts and techniques in this field has been reached during the last two decades. Electronic pill box monitors or electronic compliance monitoring devices (ECMDs), which enable monitoring of the daily dosing by recording the time of each opening of the pill container or taking a tablet out of a blister pack, became available in some research and clinical settings. They have markedly advanced our knowledge of medication-taking behaviour and its risk factors.[11,12] At the same time, the new key paradigm of understanding and management of medication compliance or adherence was introduced. According to

that, the prescription is really a contract between the patient and the physician and both are really responsible for the medication-taking; hence, they should interact on the matter in the process of treatment, in concordance with the contract.[13] Such direct compliance management *per se* (which can include measurement, feedback and counselling) may be considered and used as an active component of hypertension treatment programs to improve their outcomes. This novel approach has been referred to as "compliance measurement-guided (medication) management (CMGM) programs".[14]

Many other approaches for indirect correction of patient compliance with medication during hypertension management have been suggested, and some of them were evaluated in a systematic manner. The Cochrane review by Schroeder *et al* [15] finalized in 2004 concluded that, among many approaches tested, only reducing the number of daily doses appears to be effective in increasing adherence, but not BP control. The authors claim motivational strategies and complex interventions appear promising which should be addressed in future studies and reviews. The most comprehensive systematic review by Haynes *et al*[16] on interventions for enhancing medication adherence in chronic diseases (including hypertension) declared current methods of improving adherence are mostly complex, but not very effective. It is concluded high priority should be given to fundamental and applied research concerning innovations to assist patients to follow medication prescriptions for long-term medical disorders.

In general, there is growing, but still insufficient evidence as to how care for hypertensive patients should be organized and delivered in the community to help improve BP. A recently updated Cochrane systematic review provided a partial answer to this question.[17] However, although the authors offered general conclusions about the usefulness of "an organized system of regular follow-up and review of hypertensive patients" where antihypertensive drug therapy should be implemented by means of a "vigorous stepped care approach," they otherwise failed to focus on

patient compliance issues. Another recent and more specific systematic review of team-based care interventions in hypertension management involving nurses or pharmacists revealed that such strategies are effective to improve BP control.[18] In this meta-analysis, several individual components, including medication compliance assessment, were indirectly associated with improvement in BP.

Different concepts and designs of integrated care (pharmaceutical care, nurse-led care, team-based care) have been suggested to improve effectiveness of chronic disease management.[16-18] Identification and systematic evaluation of essential and most efficacious components of proposed integrated care approaches is necessary, taking into account the high resource-consuming nature of such programs, problems of their transferability and feasibility in different health care systems and diverse populations. Further research evaluating the role of specific components of complex interventions aimed to improve BP control is therefore promising. However, among the systematic reviews published in recent years and looking at different adherence-enhancing approaches[15-20] no one, up to our best knowledge, primarily and comprehensively addressed effectiveness of immediate compliance management (measurement augmented by feedback to stakeholders and counselling) as an active intervention or health technology.

The primary objective of this review was to assess the evidence of the effectiveness of CMGM interventions in treating adults with essential hypertension.

Methods

Compliance operational definitions

In this review the terms "patient compliance" and "patient (medication) adherence" were considered as synonyms. Under these terms we mean "the extent to which a patient's behaviour, with respect to taking medication, corresponds with agreed recommendations from healthcare providers".[21] We therefore assumed (but do not limit to) the following approaches of compliance measures: subjective methods (e.g. patient interview, patient diaries, patient self-questionnaire); direct methods (e.g. analysis of biomarkers in bodily fluids); indirect methods (e.g., physiologic markers, pill counts, pharmacy claim data (prescription refills) and ECMDs.[22] We were ready to consider any compliance expressions, including binomial (Yes or No), ordinal (full, partly, non-compliance) or continuous (e.g., % of the total dose prescribed in a given period of time) compliance measures. The scope of the review was CMGM or immediate compliance management as an intervention, under which we implied several components: compliance measurement (monitoring), providing a feedback to the patient (and/or to his/her physician) on his/her dosing history, and individual counselling provided by a health professional and tailored by contemporary medication taking behaviour.

Criteria for considering studies for this review

PICOS (population – intervention - comparators – outcomes – study design) paradigm of the systematic review is briefly summarized in Appendix 1.

The population of interest was composed of adult patients (aged 18 years or over) with verified essential (primary) hypertension of any stage / grade eligible for BP lowering drug treatment (treated or not previously treated) in a primary care, outpatient or other community setting. Studies of non-pharmacological treatment were not included.

We considered published studies of any duration with CMGM as intervention designed to estimate and therefore enhance patient compliance with a medication regimen with the final aim to improve outcomes in hypertension. At least the compliance measurement component must be included in a CMGM program and may be addicted with feedback and counselling.

Different strategies or combinations of components of CMGM may be compared in one study or a CMGM intervention may be compared with no such intervention or "usual care" (UC). Studies with different comparators (e.g. with identical compliance management in study arms) were excluded.

Studies were included if they reported at least one of the next groups of hypertension management outcomes: mortality (cardiovascular, non-cardiovascular, total); morbidity (cardiovascular – stroke, myocardial infarction; non-cardiovascular); BP changes / control which we supposed may be expressed via (1) mean systolic BP (SBP) and/or mean diastolic BP (DBP) values; (2) mean SBP (mean DBP) changes (delta); (3) reaching pre-specified BP threshold (according to a particular study); changes in structure and function of target organs (the heart, kidney, brain, vessels); rate and patterns of adverse reactions (led or not led to withdrawals); organizational outcomes: important features of management (rate of hospital admissions, number of visits to general practitioners, consultant physicians, any other caregiver services, medication regimens changes, etc.); humanistic or patient-reported ones (health-related quality of life, patient satisfaction, patient preferences); economic outcomes. As the secondary outcome, we were ready to analyze compliance with medication *per se* (including any definition of compliance / adherence and noting how this was defined and measured in each study). However, trials reported compliance data only as pre-specified primary outcomes were not included.

The following study designs were considered: RCTs (patient-randomized, cluster-randomized or quasi-randomized trials); cohort studies with or without controls (matched, unmatched, historic or internal). Secondary publications and interim reports were excluded.

Search methods for identification of studies

Original studies eligible for inclusion in the review were identified by an all-language search of all articles in MEDLINE (1980 to July 2010), EMBASE (1980 to July 2010), and the Cochrane Central Register of Controlled Trials (CENTRAL) (1980 to July 2010) via OVID platform.

A systematic search strategy was applied with use of a series of topic terms including hypertension/BP, patient compliance/adherence, reflecting pre-specified CMGM components and study designs (The principal strategy which was used for MEDLINE search is in Appendix 2). As a component of the search strategy, a previously validated original research string of terms was used.[23] Similar thinking was used also for search of EMBASE and CENTRAL databases. Articles published before 1980 was excluded regarding this date restriction as appropriate given changes in hypertension guidelines and clinical practice over the past three decades. No language restrictions were applied. The most recent comprehensive search for each database was performed on 7 August, 2010.

Additionally, we handsearched proceedings of the International Society of Hypertension, American Society of Hypertension & European Society of Hypertension in 2008 – 2010 for unpublished / ongoing studies. We also searched the reference lists of included papers and former reviews on compliance issues in hypertension management to identify additional citations. We planned to contact some study authors if important questions arise and reserved an option to contact experts in the field about other relevant trials or unpublished material.

Study selection

Two investigators (SG and IF) screened the retrieved records (a title and abstract) independently. Both reviewers were physicians by qualification, holding PhD degrees in cardiology (SG) and clinical pharmacology (IF); one was a qualified hypertension specialist (SG). Each reviewer indicated whether a citation is potentially relevant (i.e. appearing to meet the inclusion criteria), is clearly not relevant, or gives insufficient information to make a judgment. Printed copies of all potentially relevant citations were obtained.

Both investigators assessed copies of all presumably relevant articles independently according to the above criteria. An option to appeal to a third reviewer was reserved in case of disagreement. Every opinion differences were then resolved by discussion and consensus making. To be included in the review, a study had to meet our selection criteria and had not to meet any exclusion criterion.

Data extraction

The information was collected with use of a structured data extraction form (Appendix 3). The form was developed with use of a prototype recommended by the Center for Reviews and Dissemination.[24] It was pilot-tested on 4 randomly-selected included studies and refined. Data extraction was undertaken by the same two independent reviewers. The source and the authors of publications were not blinded. The data obtained in duplicate were then compared and discussed; consensus data were used in the review.

Quality assessment

A special study quality evaluation form was developed to assess and present methodological quality characteristics of included studies in a descriptive format (Appendix 4) based on the Cochrane risk of bias tool,[25] thereby providing an accessible and objective summary. The same two reviewers provided data for the form independently and in duplicate, with further discussions and consensus making. Additionally, overall judgment on study quality was made with use of a four-point continuum ("high", "moderate", "low" or "very low") according to the grading system developed by CHERG Review Groups on Intervention Effects[26] (Appendix 5). Typically, RCTs received an initial grade of "high", observational studies (OS) received an initial grade of "low" (in case of large well-designed cohort studies – "moderate"). An initial score may be downgraded in case of important risk of biases, or, alternatively, a score may be upgraded one level if the researchers either controlled or accounted for all plausible confounders that would have modified the effect of the intervention on the health outcome.

As significant heterogeneity in studies design, methods and outcomes measures was anticipated, no quantitative synthesis (meta-analysis) was planned. A narrative approach to data synthesis was adopted. A checklist of items to include when reporting a systematic review in accordance with the PRISMA guidelines[27] was filled and submitted along with the full text of the review (Appendix 6).

Results

Study selection

The results of the review process with reasons for exclusion are displayed as a flow diagram (Figure 1, p.10). The original database searches and reference screenings identified 752 titles and abstracts; 688 were excluded after screening the abstract. Full-text copies of 64 papers were obtained and assessed for eligibility. The most common reasons for exclusion were a study design not intended to compare groups with and without CGMM interventions (or their different components); a study design or report not included compliance measurement. A total of 12 papers reporting 13 studies met the inclusion criteria.[28-39] One study had a complex structure with 2 phases of completely different design and in the review context they were considered separately.[34]

Study characteristics

Table I (pp. 13-17) illustrates an overview of study characteristics. The studies (5 observational ones, 2 cluster-RCTs, 6 - RCTs) incorporated a total population of approximately 2150 patients with hypertension, with study arms ranging in size from 18[35] to 219.[39] The trial populations were relatively small, six trials included less than 100 patients in all arms.[28,30-32,35,38] Twelve studies were single centered, and only one was multicentered.[33] Five studies were conducted in the United States;[28,29,34,37] all but one[28] were devoted to aspects of integrated care, including three related to complex team-based interventions involving pharmacists.[34,37] Of the non-USA trials, four were Swiss-based, generated by a single research center;[30-32,37] others were conducted in Spain,[33] Germany,[35] Netherlands[36] and Poland.[39] Wherever funding was reported, trials were frequently supported by pharmaceutical companies[32,33, 35,38,39] or independent sources.

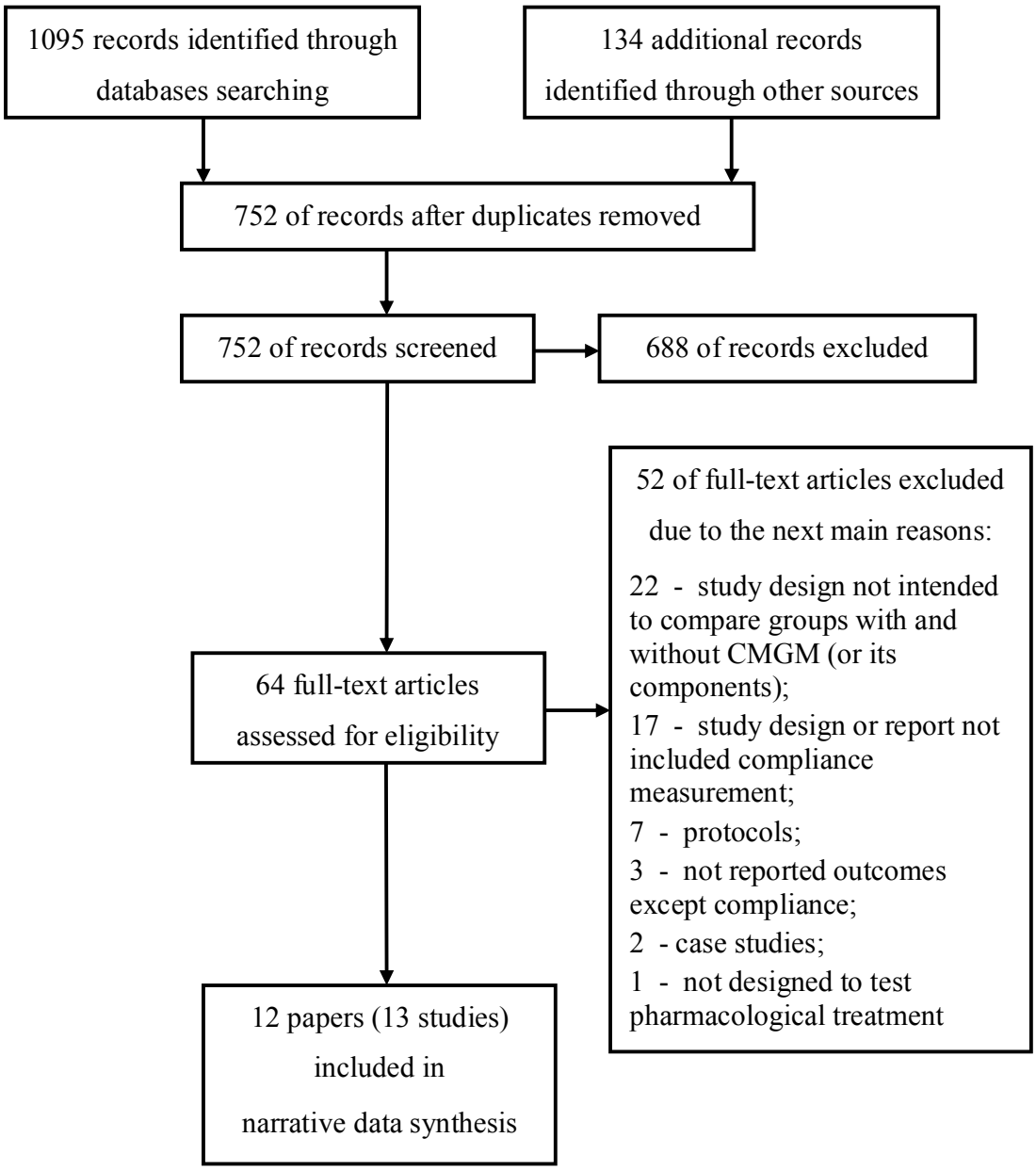

Figure 1 Flow diagram of study selection

All studies included patients with mild-to-moderate hypertension, predominantly treated, but uncontrolled, with different degree of treatment regimen intensity. Only three studies included a portion of previously untreated patients.[33, 37,39] The term for which patients had been diagnosed with hypertension was not stated in any study. Two trials included exclusively elderly patients with multiple chronic conditions and medications,[29,34] one of them included predominantly male veterans.[34] Only four trials[29,32,34,37] reported patients' ethnic origin, these were all predominantly white. Information about baseline level of patient compliance from different sources was available in four studies.[29,34,36,37] Six trials were performed in primary care settings,[28,29,33,36,38,39] seven - in specialized conditions of tertiary care (university clinics, hypertension units).[30-32,34,35,37]

With regard to the use of antihypertensive medications according to treatment plans during a study period, approaches used were quite different in nature and activity. In the studies of McKenney *et al*[28] and Waeber *et al*[30] drug treatment regimens were stable throughout the study arms. In three trials medication changes by physicians were permitted, but not specified;[29,34] in a trial by Marquez Contreras *et al*[33] a pre-specified standardized algorithm of drug regimen change based on clinical guidelines was implemented in all patient groups. In three trials pre-specified treatment strategy was based on the introduction in the treatment plan of a contemporary once daily medication (angiotensin II receptors antagonist) with option of addiction / changes of other medications according to a pre-specified algorithm[33] or at physician's will.[35,39] In a study by Wetzels *et al* [36] ECMD use for two months without medication changes was compared with UC care during which medication changes were permitted. In two observational before-and-after studies of similar designs by Bertholet *et al*[31] and Burnier *et al*[32] electronic monitoring was performed for one or two months without drug adjustments, and then elective monitoring (in case of previous non-optimal compliance) was combined with drug regimen adaptation if needed. Finally, in two studies of team-based care by Carter *et*

al[37] and Santschi *et al*[38] clinical pharmacists, according to trial designs, played a very active role to motivate treating physicians for treatment regimens optimization following current guidelines; and in the longest up to date RCT by Santschi *et al*[38] developed on the experience of previously mentioned observations,[31,32] during the first two months treatment changes were not permitted in all arms, followed by free drug changes in all arms on discretion of a general practitioner.

Seven trials employed an ECMD as compliance management intervention;[28,30-32,35,36,38,39] in the rest of studies pill counts or patient self-reports were used as a CMGM component (addicted with some feedback in intervention group(IG)), and as a surrogate pre-specified outcome.[29,33,34,37] Regarding the nature of CMGM interventions, five studies tested solely compliance management as intervention, all exclusively with use of an ECMD.[30-32,36,39] The others were devoted to complex interventions including certain CMGM as a component, in companion with patient self-control activities,[28] education and/or motivational counselling,[29,33, 35] under the frame of pharmaceutical care[34] or physician/pharmacist team-based care.[37,38] No placebo-compared (sham compliance management) studies were found. One study compared different CMGM approaches (compliance monitoring with and without feedback);[35] in two studies UC addicted with compliance measurement (pre-specified as an outcome) was used as a comparator;[37,39] in one study of prolonged pharmaceutical care by Lee *et al*[34] a CG had recent long-term exposure to the same complex intervention with CMGM component. The frequency of compliance feedback to the patient across the trials ranged from once in 1 or 2 months[31,32] to everyday reminding in case of an interactive (with audio/visual reminder) ECMD use.[28,35,39] Two studies by Lee *et al*[34] and Wetzels *et al*[36] dealt with the problem of persistence of an effect of compliance intervention after its discontinuation. The majority of studies had at least 6-month follow-up, [28,29,33,34, 37-39] but only one with a small sample size reached the period of 12 months.[38]

Table I Characteristics of included studies

Reference (Study acronym)	Design	Duration	Total N of patients (by arms)	Hypertensive population	Setting	Components of CMGM as intervention	C measures	Comparator(s)	Pre-specified outcomes
				CMGM alone					
Bertholet *et al* [31]	OS without control (before-and-after)	Up to 2 months + up to 2 months	71	Treated (1-3 drugs), uncontrolled	Tertiary care, hypertension center	Monitoring, every day for 1 or 2 months + feedback to patient and physician at the end; then elective monitoring, every day	ECMD for each drug, taking C*	---	Office BP values, changes, control rate
Burnier *et al* [32]	OS without control (before-and-after)	2 months + 2 months	41	Resistant to triple therapy	Tertiary care, hypertension center	Monitoring, every day for 2 months + feedback to patient at 2 months; then elective monitoring, every day	ECMD for each drug, taking C*	---	Office BP values and changes, control rate+ ABPM values
Christensen *et al* [39]	Cross-over RCT	6 months + 6 months	219 /179	Untreated or ineffectively treated	Primary care	IG: Monitoring, every day + feedback to patient (reminding), every day CG: None of above	IG: ECMD for one drug, taking C, dosing C**, timing C***, drug holidays****; IG, CG: patient self-reporting	UC with C self-reporting	Office BP values and changes

Reference (Study acronym)	Design	Dura-tion	Total N of pati-ents (by arms)	Hyper-tensive popu-lation	Setting	Components of CMGM as intervention	C measures	Compa-rator(s)	Pre-specified outcomes
Waeber *et al* [30]	OS without control (before-and-after)	3 months	35	Treated, uncont-rolled	Tertiary care, hyperten-sion center	Monitoring, every day for 3 months + feedback to patient	ECMD for one drug, taking C*	---	Office BP values
Wetzels *et al* [36]	RCT	2 months + 3 months	168/90	Treated, uncont-rolled	Primary care	IG: Monitoring, every day for 2 months + feedback to patient at 2 months CG: None of above	IG: ECMD for each drug, taking C*	UC	Office BP values, changes, control rate; drug regimen changes
CMGM in complex interventions									
Friedman *et al* [29]	RCT	6 months	133/134	Elderly, treated, uncont-rolled	Primary care	IG: Self-report + feedback to physician, every week CG: None of above	IG: Patient-self report to telephone-linked computer system; IG, CG: Pill count#	UC	Office BP values, changes; Patient satisfaction; Incremental cost-effectiveness
Marquez Contreras *et al* [33] (ETECU M-HTA)	Multi-center RCT	6 months	184/172/ 182	Treated and un-treated, including newly	Primary care	IG(Telephone) Self-report + feed-back to patient, 3 times over study IG(Mail), CG:	IG (1): Patient-self report during telephone interview; IGs, CG: Pill	UC	Office BP values, changes

Reference (Study acronym)	Design	Dura-tion	Total N of pati-ents (by arms)	Hyper-tensive popu-lation	Setting	Components of CMGM as intervention	C measures	Compa-rator(s)	Pre-specified outcomes
				diagnosed		none of above	count# (only two drugs)		
McKen-ney *et al* [28]	RCT (2 phases)	12 weeks + 12 weeks	70	Treated, uncont-rolled, mostly elderly	Primary care	IG: monitoring, every day + feedback to patient (audiovisual reminding), every day	IG: ECMD as timepiece cap on vials of each drug with reminding (alarm + flash); IG, C: pill count#	UC (Phase I); UC, ECMD + diary (cards) of office BP; ECMD + home BP measure-ment with cards (Phase II)	Office BP values
Mengden *et al* [35]	OS with quasi-ran-domized compo-nent	4 weeks run-in + 8 weeks	18/20/ 24	Treated, resistant on >2 drugs	Tertiary care	Group A and B: Monitoring only, every day; Group C: Moni-toring with feed-back to patient (visual remin-ding),every day	All groups: ECMD, taking C*, dosing C**	C moni-toring without feedback	Office and home BP values and changes + ABPM values, changes and control rates

Reference (Study acronym)	Design	Dura-tion	Total N of pati-ents (by arms)	Hyper-tensive popu-lation	Setting	Components of CMGM as intervention	C measures	Compa-rator(s)	Pre-specified outcomes
				CMGM in integrated care environment					
Carter *et al* [37]	Cluster RCT	9 months	101/78	Mostly treated	Tertiary care	IG: Measurement + feedback to clinical pharmacist at baseline, 2, 4, 6, 8, 9 months CG: Measurement only at the same time	IG, CG: Pill count##	UC with increased surveil-lance and informa-tion sup-port, C measure-ment	Office BP values, changes, control rate + ABPM values; drug regimen changes; adverse effect score
Lee *et al* [34] (FAME, Phase I)	OS without control (before-and-after)	2 months run-in + 6 months	159	Elderly, mostly men, treated	Tertiary care	Measurement + feedback to patient by clinical pharmacist, every 2 months	Pill count#	---	Office BP values, changes
Lee *et al* [34] (FAME, Phase II)	RCT	6 months	83/76	Elderly, mostly men, treated under pharma-ceutical care	Tertiary care	IG: Measurement + feedback to patient by clinical pharmacist, every 2 months CG: Measurement only at baseline and at the end	IG, CG: Pill count#	UC with previous recent pharma-ceutical care	Office BP values, changes

Reference (Study acronym)	Design	Dura-tion	Total N of pati-ents (by arms)	Hyper-tensive popu-lation	Setting	Components of CMGM as intervention	C measures	Compa-rator(s)	Pre-specified outcomes
Santschi *et al* [38]	Cluster RCT	12 months	34/34	Treated, uncont-rolled	Primary integrated care (general practitioners and pharma-cists)	IG: Monitoring, every day (elective after 2 months) + feedback for patient and physician via pharmacists at 2, 4, 6 and 12 months; CG: None of above	IG: ECMD for one drug, taking C*	UC	Office BP values, changes; drug regimen changes

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; C, compliance; CG, control group, CMGM, compliance measurement-guided management; ECMD, electronic compliance monitoring devices; IG, intervention group; OS, observational study; RCT, randomized controlled trial; UC, usual care.

*Number of days (in percent), during which the prescribed number of doses were recorded as taken by electronic device.
**(number of days with the correct number of device activations during a certain period / number of days in the period)x100.
***(number of correct dosing intervals during a certain period / number of dosing intervals during the period)x100; correct dosing intervals are prescribed dosing interval $\pm$25%.
**** (number of calendar days without device activation during a certain period / number of calendar days in the same period) x100.
#Percent of total number of tablets (capsules, patches) dispensed minus the total number counted in the audit divided by that should be taken by each subject during the period analyzed.
##Percent of predicted doses measured at each visit.

Table II Quality assessment of included studies

Reference (Study acronym)	Truly randomized	Allocation concealment	Blinding of outcome assessors	Eligibility criteria specified	Hypertension verification / description	Baseline comparability*	Treatment comparability by groups	Difference in organization of care	Confounding addressed	Sample size adequate	Withdrawals rate <20%	Withdrawals reasons specified	ITT analysis	Overall quality estimation
CMGM alone														
Bertholet *et al* [31]	No	NA	No	Yes	§	NA	NA	NA	NA	?**	Yes	Yes	No	Low
Burnier *et al* [32]	No	NA	No	Yes	§	NA	NA	NA	NA	?**	Yes	Yes	No	Low
Christensen *et al* [39]	Yes	?	No	Yes	§ [a]	Yes	? [b]	No	No	?	No	Yes[c]	No	Mode-rate
Waeber *et al* [30]	No	NA	No	Yes	§	NA	NA	NA	NA	?**	Yes	Yes	No	Low
Wetzels *et al* [36]	Yes	Yes	Yes [d]	Yes	§ [e]	§[f]	No	Yes	Yes	Yes	Yes	Yes	Yes	Mode-rate
CMGM in complex interventions														
Friedman *et al* [29]	Yes	Yes	Yes	Yes	§[k]	Yes	?	?	Yes	? **	Yes	No	No	Mode-rate
Marquez Contreras *et al* [33] (ETECUM-	Yes	Yes	?	Yes	§	Yes	No[o]	No	No	Yes	Yes	No	No	Mode-rate

Reference (Study acronym)	Truly randomized	Allocation concealment	Blinding of outcome assessors	Eligibility criteria specified	Hypertension verification / description	Baseline comparability*	Treatment comparability by groups	Difference in organization of care	Confounding addressed	Sample size adequate	Withdrawals rate <20%	Withdrawals reasons specified	ITT analysis	Overall quality estimation
HTA)														
McKenney *et al* [28]	?	?	No	Yes	§	No***	?	Yes	No	? **	No	Yes	No	Low
Mengden *et al* [35]	No	No	No	§[p]	§	§[q]	No[r]	No	No	? **	Yes	Yes	No	Low
CMGM in integrated care environment														
Carter *et al* [37]	Yes	No	Yes	Yes	§	§[g]	No[h]	Yes[i]	Yes	Yes[j]	Yes	Yes	Yes	High
Lee *et al* [34](FAME, Phase I)	No	NA	No	Yes[l]	§	NA	NA	NA	NA	? **	Yes	Yes	No	Low
Lee *et al* [34] (FAME, Phase II)	Yes	Yes	No	Yes[k]	§	§[m]	No[m]	Yes[n]	Yes	? **	Yes	Yes	Yes	High
Santschi *et al* [38]	Yes	No	No	Yes	§	§[s]	No[h]	No	Yes	No[t]	Yes	No	Yes	Mode-rate

? , Cannot tell; §, partially; CMGM, compliance measurement-guided management; NA, not applicable.
* Based on presented criteria.
** Calculations not reported.
***Groups were unbalanced on baseline DBP.
[a] Described only as untreated or ineffectively treated.
[b] Based on telmisartan in all groups.
[c] Potentially fraudulent data identified.
[d] Measurements at baseline performed by physician, throughout the study by research nurse.
[e] Local definition of hypertension according to BP level.
[f] Higher proportion of men in CG.
[g] Higher baseline medication adherence score in CG; addressed in analysis.
[h] Antihypertensive treatment regimens actively changed during study.
[i] Number of visits differ between groups; addressed in analysis.
[j] Did not reach the most conservative estimate.
[k] More then 70% of sample suffered from isolated systolic hypertension .
[l] Based on age and number of medications (4 or more); hypertensives presented more then 90% of sample.
[m] More medications for psychiatric problems and angiotensin-converting enzyme inhibitors in IG; addressed in analysis.
[n] According to study design, participants of IG (pharmaceutical care) received a regular follow-up, wile controls did not.
[o] Candesartan-based treatment; addition of diuretic was lower in CMGM-group.
[p] Exclusion criteria not specified.
[q] Prevalence of diabetes mellitus differed between groups.
[r] In 2 groups candesartan/hydrochlorothiazide was introduced.
[s] Lower age, higher systolic and lower diastolic BP in CG; addressed in analysis.
[t] Not calculated; based on authors' assumption.

The commonly used pre-specified outcome of the trials was the effect of the interventions on direct measures of office BP, in seven ones BP control rates was also evaluated;[31-33,35-38] and three studies used repeated ambulatory blood pressure monitoring (ABPM) as the most objective measure of BP changes.[32,35,37] Three trials also pre-specified and assessed drug regimen changes as an outcome,[36-38] one reported changes in adverse effect score[37] and only one study by Freedman *et al*[29] partially addressed incremental cost-effectiveness of as well as patient satisfaction of the intervention using a telecommunication system.

Study quality assessment

Table II (pp. 18-20) presents the outcomes of the study quality assessment. Overall, the methodological quality of the included trials varied from low in case of OS[30-32,34,35] to high[34,37] with tendency to improvement of the quality of reporting over time. As a rule, quality criteria were not met due to lack of reporting, rather then due to specific reporting of inadequate methods.

All RCTs stated that patients were randomly allocated to treatment groups and all but one[28] described the method of randomization; however, only four trials[29, 33,34,36] supplied sufficient details about sequence generation indicating allocation of participants was adequately concealed; in other cases to make such a judgment was not possible. With regard to blinding, it would be unreasonable to expect patients or personnel to keep blinding as to allocation in trials incorporating CMGM due to very different comparator groups. It should, however, be possible to blind assessors, but only three trials[29,36,37] provided positive information regarding the blinding of assessors. No trial reported any assessment of blinding procedures.

All trials reported patient eligibility criteria, and baseline comparability was achieved or partially achieved with exception of one study[28] where important differences in baseline DBP between study arms were not addressed in analysis. Overall, the studied disease description was not comprehensive, with provision of

some aspects that differed across studies. Details about hypertension diagnosis verification, in part, about identification and exclusion of cases with secondary hypertension, were not reported in any study. Studies performed at university clinics or hypertension centers recruited very selective samples of participants referred to tertiary care services with possible important peculiarities in nature of the disease and compliance issues.[30-32,34,35,37]

Co-interventions in case of CMGM composed of complex experimental approaches were well reported. In some cases additional concerns about validity of results generated by confounding in organization of care were noted. As it was indicated, in a study by Wetzels *et al*[36] medication changes in the CG were permitted for the first 2 months, although in the IG they were not; this could have a major impact on conclusions showing fewer drug changes under intervention (ECMD) for the whole study period of 5 months. In other studies physicians could change some or all drug regimens at their free discretion throughout a study and its arms without appropriate documentation, making impossible to control such confounding.[31,32,35,39] In contrast, in two studies devoted to effectiveness of physicians / pharmacists collaboration active medication changes throughout the studies were recorded and reported as well as addressed in statistical analyses.[37, 38]

The precision of evaluation of the most common outcome – office BP - was different due to fluctuations of measurement techniques and calculations of BP level data across studies. Measurements performed by the physician at baseline, and then throughout the study by a research nurse might introduce a “white coat” component in baseline BP levels and hence overestimate registered BP changes.[36] In one study by Christensen *et al*[39] employed everyday compliance monitoring via an ECMD a subjective method of compliance measurement (patient self-questionnaire filled once in 6 months) was used as a reference outcome measure which probably compromised data analyses and study conclusions.

Intention-to-treat (ITT) analyses were declared and performed in five studies.[34,36,37,38] All but three trials[29,33,38] reported numbers of attrition and exclusions with reasons. Only studies by McKenney *et al*[28] and Christensen *et al*[39] were included less then 80% of enrolled participants in the final analysis at least in some treatment arms. All reports were free of suggestion of selective outcome reporting.

Effectiveness of interventions

The preceding sections indicate that the included trials were of different quality and the interventions and comparators were heterogeneous. These factors argue against any statistical meta-analysis of the data; a narrative summary of results was therefore compiled. This section presents a narrative summary of intervention effects on the most common and clinically important outcome - BP - grouped by CMGM type (i.e. CMGM alone or in combination with another approaches to improve compliance and / or treatment outcomes; ECMD or other compliance measure) and by comparator: UC, UC with some advances, and different composition of CMGM components. Special attention in description of CMGM effectiveness was paid to nature and changes of antihypertensive medication during investigation according to a study design. Levels, changes of compliance and their relation to the outcome of interest were also addressed. Table III (pp. 30-36) summarizes these findings.

CMGM alone

In three OS[30-32] with obligatory ECMD use for 1-3 months significant improvement of BP levels and control rates were achieved in previously uncontrolled patients without any changes in medications. It was demonstrated under polypharmacy conditions[31,32] as well as under monotherapy.[30] These positive results were accompanied by extremely high compliance rate exceeding 90%. Continuation of elective compliance management in some patients and medication

adjustments in others under investigators' discretion beyond 1-2 months provided additional benefit in one study.[31] This benefit was not confirmed by 4 months in another study with use of ABPM.[32]

Two RCTs compared CMGM with use of ECMDs with UC.[36,39] In the study of Wetzels *et al*[36] medication adjustment in CG of previously uncontrolled hypertensives resulted in more favourable BP changes and control rate than in IG of CMGM without drug regimen optimization during the first 2 months, despite high compliance rate (more then 95%) in IG. When CMGM was stopped and medication changes were permitted in both groups, BP differences between study arms were disappeared by 5 months. The study sample was comprised of patients with high prevalence of persons with previous satisfactory adherence based on pharmacy refill rates.

In the RCT of Christensen *et al*[39] introduction of CMGM (ECMD with reminding) was compared in crossover fashion with UC against the background of treatment switch to telmisartan-based regimens. After the first six months, the groups of CMGM and UC were not different in BP changes with tendency to a higher rate of self-reported compliance in the IG. After the next 6 months, no significant BP differences were occurred between the group of UC after initial CMGM and the group of postponed CMGM. The study participants consistently reported high levels of compliance that were not corroborated by electronic monitoring data of telmisartan use (52% after 6 months of ECMD use; 38% after 12 months including 6 months of postponed ECMD use). The study is characterized of extremely high dropouts and withdrawals rates; in part, certain electronic monitoring data were excluded from the analysis due to doubts about their authenticity.

CMGM as a component of complex interventions

In four studies of original complex designs CMGM combined with some other activities to increase compliance was tested; in two of them ECMDs were implicated. In the two-phase RCT of McKenney *et al*[28] with older participants, the possibility of improvement of both BP level and compliance (based on pill counts) under CMGM (with use of reminding ECMD) compared with UC was initially demonstrated. Then the whole population was repeatedly randomized to groups under UC, with ECMD alone, ECMD along with structured diaries to be filled by patient and finally ECMD with home BP monitoring and diaries. Further decrease in SBP was documented following 12 weeks under all interventions without significant intergroup differences but not in controls (UC); the study arms were unbalanced in baseline DBP. The investigators aimed to conserve the treatment regimes throughout the study; in case of changes participants were excluded from the analysis.

Mengden *et al*[35] studied several approaches in management of resistant hypertensives in one small short-term trial with a sophisticated design. After initial four weeks of ECMD use on standard drug regimens, participants with sufficient BP control as reflected by ABPM and BP self-monitoring (29%) were observed for the next eight weeks; in other patients a drug was replaced by fixed combination of candesartan and hydrochlorothiazide and they were divided into groups with ECMD with and without visual reminding function (everyday feedback to patient) along with continuing BP home self-measurement. The group equipped by reminding ECMD also received a structured hypertension teaching program. Compliance dynamics in initial four weeks were corresponded to BP control, with remarkable negative drive in uncontrolled participants. Changes in management resulted in stable compliance levels, improvement of BP and BP control rate (39%), without significant differences between groups with and without feedbacks to patients.

Friedman *et al*[29] tested a telephone linked computer system conversing weekly with elderly patients in their homes between office visits to their physicians. Computer-controlled speech included questions about compliance and gave feedback; patients communicated using the touch-tone keypad on their phones. Feedbacks on patent's compliance was stored and forwarded as a printed report to his/her physician on a regular basis, and 40% of physicians discussed regularly the reports with their patients. Compared with UC, such type of CMGM resulted in marked positive changes in compliance indexes in spite of high pre-study levels estimated; however, they translated in significant DBP improvement only in previously non-adherent patients.

In the multicenter RCT of Marquez Contreras *et al* [33] telephone intervention (three telephone calls during the study made by expert nurses, which included patient compliance self-reports and their evaluation with motivation to desirable behaviour) was compared with mail intervention (three mailings with health and compliance education and reminding of the scheduled visits) and with UC. Standardized treatment step-care approach based on candesartan was implemented throughout the study. In result, compliance rate was higher in IGs compared with UC; the most pronounced positive BP changes was revealed in CMGM (telephone) group which were significantly different as compared with UC.

CMGM in integrated care environment

Four recent studies with the longest duration investigated different complex approaches reflecting and testing modern popular concepts of pharmaceutical care or team-based care as a tool to improve long-term management of chronic diseases.

In two phases of FAME study[34] the influence of pharmaceutical care on BP control was evaluated in elderly patients under multiple drug regimens for treatment of hypertension and concomitant cardiovascular disorders. Besides compliance

measurement and feedback, pharmaceutical care included simplification of medication delivery with use of customized blister packs and patient education efforts. In prospective 6-month observation (Phase I) patient compliance rate was markedly improved in pharmaceutical care group which resulted in SBP but not DBP reduction (By the way, BP values were not substantially increased at the Phase I entry). At entry to Phase II, patients were randomized to continued pharmaceutical care versus UC. Prolongation of the pharmaceutical care with CMGM component till the next 6 months maintained compliance rate at the same high level. It resulted in more pronounced SBP changes then in the CG which experienced the same intervention in previous 6 months. In this CG, compliance rate was significantly lower than in pharmaceutical care group, but significantly higher than the one at the Phase I entry. It is deserved attention that prolonged pharmaceutical care did not demonstrate additional benefit in Phase II for cholesterol reducing medications.

In the cluster RCT of Carter *et al*[37] the ability of a specific type of physician/pharmacist collaboration to improve BP control was studied. In the IG physicians and clinical pharmacists underwent team-building exercises; clinical pharmacists provided an educational patient interview at baseline and performed repeated meetings with a patient at pre-scheduled office visits and more often, if needed, in person or via telephone. Main contents of pharmacist/patient contacts were postulated as efforts to improve compliance based on its evaluation of a research nurse, and development of recommendations to the treating physician for drug regimens changes according to contemporary clinical guidelines, at the pharmacist's discretion. Previous compliance rate in IG was significantly lower then in controls; it was improved during the intervention, so the differences disappeared. ABPM as well as office BP data were significantly better in IG which were reflected also by remarkably higher BP control rate. Clinical pharmacists were very active in making treatment recommendations to physicians, especially during the first 2 months of observation, and 96% of suggestions where accepted by physicians. In contrast,

specific recommendations on compliance were rarely developed by pharmacists. Significantly more frequent changes in medications regimens in IG resulted in significantly higher mean number of medications compared to controls, but without rise in adverse effect scores in both study arms.

The only one study of 12-month duration but small sample size[38] aimed to evaluate clinical efficacy of CMGM with ECMD as a component of integrated care with participation of pharmacists. After 2 months of obligatory use of ECMD in IG without drug regimen changes in both intervention and control arms, elective CMGM (depending on patient compliance data) as well as treatment changes were undertaken by treating physicians. Pharmacists were involved in ECMD handling, printing the adherence report during each patient visit, discussing the report with the patient and transmitting of it to the physician. Intervention group differed from controls in BP levels and control rates only after 4 months of the study; compliance rate in monitored patients was very high during the whole study term, and physicians tended to modify more frequently antihypertensive treatment in the IG.

Non-hemodynamic outcomes of CMGM

Three trials that pre-specified and assessed drug regimen changes as an outcome[36-38] reported conflicting results. Wetzels *et al*[36] revealed fewer drug changes and less drug use under CMGM, but these results may be related to baseline differences in antihypertensive drugs numbers between arms as well as to the study design not permitted drug changes in the first two months in the IG. In the Carter *et al*[37] were documented more intensive drug changes and more pronounced increase in mean drug numbers per day in IG, which may be attributed to active treatment regimen counselling generated by clinical pharmacists rather then CMGM per se. Finally, in the study of Santschi *et al*[38] more frequent increase in numbers / dosage of antihypertensive medication in CMGM group were occurred which was not translated in sustained BP control improvement.

The only one study by Freedman *et al*[29] considered problems of patient satisfaction with a CMGM program with use of a questionnaire and a visual analog scale. 69% and 54% of patients scored overall satisfaction in the upper quartile of the corresponded tools. In the same study cost-effectiveness ratio of compliance management intervention was also tested. For DBP, the cost-effectiveness ratio for the whole studied group of hypertensives was 7,39 $ per 1 mm Hg decrease after 6 months of CMGM. For non-adherent portion of patients, cost-effectiveness varied from 3,39 $ per 1 mm Hg improvement in DBP at 80% baseline adherence to 0,87 $ per 1 mm Hg improvement at 50% adherence.

Table 3 Effectiveness of interventions

Reference (Study acronym)	Medication regimen			Compliance		Blood Pressure	
	Previous drug numbers per day	**Nature of changes introduced**	**Changes in drug numbers per day**	**Previous level estimation**	**Compliance data / dynamics**	**BP levels / dynamics**	**Dynamics of BP control rate**
Electronic compliance monitoring alone with feedback							
Bertholet *et al* [31]	1 - 11%; 2 - 22%; 3 - 67%	First 1 or 2 months: no changes; next 1 or 2 months: adjusted if needed, NSp	NSp	NSp	After monitoring period of 1 or 2 months: 90,7% in subgroup with controlled BP; 92,5% in subgroup with improved BP; 91,6% in subgroup with uncontrolled BP	SBP decreased from 159±23 to 143±20* during monitoring and to 133±20* mm Hg to the end of study; DBP decreased from 104±12 to 92±15* and then to 85±12*(mean±SD)	After obligatory monitoring period: in 33,3% BP normalized (<140/90 mm Hg); in 33,3% - BP improved (ΔSBP≥10; ΔDBP≥5 mm Hg)
Burnier *et al* [32]	3; 92% of drugs – once a day	2 months: no changes; next 2 months: adjusted if needed, NSp	NSp	NSp	After 2 months: mean 93% (SD 9,3%) After 4 months: mean 94% (monitored patients)	After 2 months: ΔSBP -11,5*; ΔDBP -9,1*; After 4 months: SBP, DBP, ABPM: no additional changes	After 2 months: SBP from 0 to 32% (40% based on ABPM); DBP from 0 to 34% (25% based on ABPM)

Reference (Study acronym)	Medication regimen			Compliance		Blood Pressure	
	Previous drug numbers per day	**Nature of changes introduced**	**Changes in drug numbers per day**	**Previous level estimation**	**Compliance data / dynamics**	**BP levels / dynamics**	**Dynamics of BP control rate**
Waeber *et al* [30]	1 (mono-therapy or fixed-dose combina-tion)	No changes	No changes	NSp	80,8±20,5%	from 167,9/100,4±16,3/7,2 to 152,5/90,9± 20,9/11,5* (mean±SD)	NSp
Electronic compliance monitoring alone with feedback (reminding) vs. usual care							
Christen-sen *et al* [39]	1 - 5%; 2-3 - 28%; 4-5 - 30%; 6-7 - 35%; >7 -2% Mean 4	Telmisartan once a day; other NSp	NSp	NSp	Based on ECMD: In group using ECMD at entry: 51,8%; In group using post-poned ECMD: 38,4%, Based on self-reporting: early ECMD vs. UC: 90,6% vs.85,1% (NS); UC after ECMD vs. postponed ECMD: 88,4% vs. 86,3% (NS)	After 6 months: early ECMD vs. UC: ΔSBP -28,8 vs. -28,3 (NS); ΔDBP -13,4 vs. -13,6 (NS); After next 6 months: UC after ECMD vs. postponed ECMD: ΔSBP -6,1 vs. -5,8 (NS); ΔDBP -3,3 vs. -3,2 (NS),	NSp
Wetzels *et al* [36]	≤2 - 46% (IG),74% (CG);	2 months: no changes (IG),	Net % of patients with dose	% adherers (average refill	After 2 months: 95,3% (SD 10%), % of correct dosing	After 2 months, IG vs. CG: ΔSBP -9 vs. -15*;	After 2 months: 38,6% (IG) vs. 57,8% (CG)*

Reference (Study acronym)	Medication regimen			Compliance		Blood Pressure	
	Previous drug numbers per day	**Nature of changes introduced**	**Changes in drug numbers per day**	**Previous level estimation**	**Compliance data / dynamics**	**BP levels / dynamics**	**Dynamics of BP control rate**
	>2 - 54% (IG), 26% (CG),	adjusted if needed (CG); next 3 months: adjusted if needed, NSp	increase or drug addiction 28,9 (IG), 61,1 (CG)	adherence ≥85%) based on pharmacy records 81% (IG) vs. 77% (CG)	≥85% -95,8% (IG)	ΔDBP -6 vs. -10*; After 5 months, IG vs. CG: ΔSBP -15 vs. -15 (NS); ΔDBP -10 vs. -10 (NS),	After 5 months: 53,7% (IG) vs. 50,6% (CG) (NS)
Electronic compliance monitoring and feedback (reminding) with and without patient structured diaries and home BP measurement vs. usual care							
McKenney *et al* [28]	Mean 1,6; 1 - 46%	No changes permitted	No changes permitted	NSp	Phase I: IG: 95%; CG: 78%; Phase II: IGs: ECMD alone: 94%; ECMD + diary: 99%; ECMS + home BP + diary: >100%; UC: 79%	After Phase I: significant decrease SBP and DBP in IG, but not in CG; After Phase II: further decrease in SBP in all IGs, with tendency to be more pronounced under combined interventions; in UC: tendency to increase BP	NSp

Reference (Study acronym)	Medication regimen: Previous drug numbers per day	Medication regimen: Nature of changes introduced	Medication regimen: Changes in drug numbers per day	Compliance: Previous level estimation	Compliance: Compliance data / dynamics	Blood Pressure: BP levels / dynamics	Blood Pressure: Dynamics of BP control rate
Electronic compliance monitoring and feedback (reminding) with education vs. electronic compliance monitoring alone without feedback							
Mengden *et al* [35]	>2	4 weeks run-in: no changes After 4 weeks: Can-desartan/hy-drochloro-thiazide once a day, replaced a drug (groups B and C)	Increased from mean 2,8 to 3,7 (Group B), from 2,8 to 3,6 (Group C)	NSp	After 4 weeks: In group A with sufficient BP control was stable; in others (group B+C) - decreased over time (*) and lower then in group A (*) After 12 weeks: In group A, group B (ECMD without feedback) and group C (ECMD with feedback + education) was stable and comparable	After 12 weeks, group C vs. group B, ABPM: ΔSBP -9 vs. -10 (NS); ΔDBP -4 vs. -6 (NS),	After 4 weeks run-in, ABPM: 29%; After 12 weeks, ABPM: Group B: 39%; Group C: 39%,
Compliance measurement with telephone-based feedback and counselling vs. usual care							
Friedman *et al* [29]	Mean 1,5 (IG), 1,4 (CG)	NSp (changes permitted)	No significant changes	Mean 93% (IG), 94% (CG) by home pill	Adjusted change IG vs. CG, total population: 17,7% vs. 11,7%*;	Adjusted IG vs. CG, total population: ΔSBP -11,5 vs. -6,8 (NS);	NSp

Reference (Study acronym)	Medication regimen			Compliance		Blood Pressure	
	Previous drug numbers per day	**Nature of changes introduced**	**Changes in drug numbers per day**	**Previous level estimation**	**Compliance data / dynamics**	**BP levels / dynamics**	**Dynamics of BP control rate**
				count)	Adherent patients (took 80% or more drugs: 0,6% vs. 3,0% (NS); Nonadherent patients: 36,0 vs. 26,0*	ΔDBP -5,2 vs. -6 (NS); Nonadherent patients: ΔSBP -12,8 vs. -0,9 (NS); ΔDBP -6,0 vs. +2,8*,	
Marquez Contreras *et al* [33] (ETECUM-HTA)	NSp	Standardized stepped algo-rithm: from candesartan in the morning + hydrochloro-thiazide + calcium antagonist or ACEI	No significant differences between groups in numbers, but % of patients used diuretic was lower in telephone IG	NSp	Telephone IG vs. Mail (education) IG vs. CG: 99,1% vs. 96,6% vs. 89,6* (* by groups)	Telephone IG vs. Mail IG vs. CG: ΔSBP -31,6 vs. -22,2 vs. 22,1*(compared to Telephone IG); ΔDBP -19,7% vs. -12,9 vs. -12,7* (compared to Telephone IG),	Telephone IG: 63,3%; Mail IG: 61,3%; CG: 47,2%*(compared to Telephone IG),

Reference (Study acronym)	Medication regimen			Compliance		Blood Pressure	
	Previous drug numbers per day	**Nature of changes introduced**	**Changes in drug numbers per day**	**Previous level estimation**	**Compliance data / dynamics**	**BP levels / dynamics**	**Dynamics of BP control rate**
Compliance measurement and feedback as component of pharmaceutical care							
Lee *et al* [34] (FAME, Phase I)	Total 8,7 (SD 3,1) Antihy-perten-sive 2,52 (SD 1,15)	No pre-specified changes	No signifi-cant changes; antihyper-tensive 2,55 (SD 1,23)	61,2% (SD 13,5%)	After 6 months of pharmacy care 96,9% (SD 5,2%), absolute change 35,5%*	ΔSBP -3,3* ΔDBP -0,8 (NS)	NSp
Compliance measurement and feedback as component of pharmaceutical care vs. advanced usual care							
Lee *et al* [34] (FAME, Phase II)	Antihy-perten-sive 2,55 (SD 1,23)	No pre-specified changes	No differences between groups IG vs. CG 2,60 vs.2,61 (NS)	96,9% (SD 5,2%)	After 6 months IG (continued pharmacy care (12 months in total)) 95,5% (SD 7,7%) CG (stopped pharmacy care) 69,1% (SD 16,4%)*	IG vs. CG ΔSBP -6,9 vs. -1,0*; Δ DBP -2,5 vs. -1,2 (NS),	NSp
Compliance measurement and feedback as component of team-based care vs. advanced usual care							
Carter *et al* [37]	IG: 1,5 (SD 1,0)	IG: Active changes	IG: 2,4 (SD 0,9)	IG: 71,1% (SD 27,0%)	IG: 94% CG: 92 % (NS)	24 hour SBP before study, IG vs. CG: 135,5	IG: from 0% to 89,1%;

Reference (Study acronym)	Medication regimen			Compliance		Blood Pressure	
	Previous drug numbers per day	**Nature of changes introduced**	**Changes in drug numbers per day**	**Previous level estimation**	**Compliance data / dynamics**	**BP levels / dynamics**	**Dynamics of BP control rate**
	CG: 1,4 (SD 1,0)	according to guidelines suggested by clinical pharmacists	CG: 1,9* (SD 1,0), more frequent changes in IG	CG: 88,6 %* (SD 20,9)		(SD11,3) vs. 136,0 (SD 13,3) (NS); after study: 121,2 (9,9) vs. 131,3 (11,8)*; 24 hour DBP before study, IG vs. CG: 76,0 (9,8) vs. 76,6 (9,9) (NS); after study: 69,1 (8,6) vs. 73,7 (8,0)*	CG (with increased surveillance) : from 0% to 52,9%,
Electronic compliance monitoring and feedback as component of team-based care vs. usual care							
Santschi *et al* [38]	47% - 1 drug; IG: 2,5; CG: 2,2,	First 2 months: no changes; After: allowed, NSp	IG: more frequent increase in numbers / dosage	NSp	IG: first 2 months 96,9%; after 12 months 97,1% (in selected patients)	IG vs. CG: at 4 months 143,4 (SEM 3,9) vs. 154,3 (2,7)* mmHg; at other periods no significant differences,	IG vs. CG, at 2 months 24% vs. 18% (NS); at 4 months 38% vs. 12%*; At 12 months 21% vs. 9% (NS),

*, significant differences; ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; C, compliance; CG, control group, CMGM, compliance measurement-guided management; DBP, office diastolic blood pressure; ECMD, electronic compliance monitoring devices; IG, intervention group; NS, not significant; NSp, not specified; SBP, office systolic blood pressure; SD, standard deviation; SEM, standard error of mean; UC, usual care.

Discussion

The objective of this review was to assess the evidence of the effectiveness of CMGM procedures in treating adults with essential hypertension. We considered patient compliance monitoring, feedback and counselling as a health technology strategy designed to obtain timely information about level and dynamics of drug consumption with option to provide feedback to the patient (directly or via a health professional) to correct his/her behaviour during hypertension management. To our best knowledge, we conducted the first systematic review of effectiveness of this novel approach, reflecting the new concept of CMGM as a sole intervention or a component of complex programs of integrated care in hypertension management.

Characteristics of CMGM studies reviewed

The systematic review included thirteen trials of different designs of approximately 2150 patients with no trials reporting data beyond 12 months even though hypertension management is a lifetime process. In five trials, CMGM programs with ECMDs were used exclusively as active interventions; no trials were identified which tested sole CMGM programs with use of other compliance measurement tools like self-reporting or pill counts. The rest of trials employed various CMGM programs as a part of complex interventions. The studies differed also in nature of CMGM components, in part, in frequency and directions of feedback provided (to patients themselves, their physicians or other caregivers). Patients were described as having mild-to-moderate hypertension, predominantly treated unsuccessfully with different medication regimens. The trials used BP levels and changes as the sole main clinical outcome. This heterogeneity, combined with the insufficient quality of reporting, brought us to the conclusion that statistical analysis of the results would be inappropriate and, if presented, would be misleading. Instead, we assessed the level of evidence using trials' main results, in relation to the content and comparators of CMGM, patients' characteristics available, nature of antihypertensive drug treatment, compliance patterns and study quality. On the

whole, inconsistent trial results and the small numbers involved made generalization of results difficult. The authors of previous reviews devoted to ways of improvement of compliance and / or outcomes during hypertension management met similar problems in data handling and synthesis of findings. [15-20]

CMGM alone

It was essential to provide an initial estimate of the magnitude of the benefits and harms of CMGM as a discrete intervention before its consideration as a component of complex management programs. The revealed positive BP dynamics under CMGM with ECMDs in short-term (up to four months), mainly OSs might be solely attributed to the non-specific so-called Hawthorne effect related to inclusion in trials.[40] This effect means subjects may improve their behaviour regarding medications being experimentally measured simply in response to the fact that they are being studied, not in response to any particular experimental manipulation.[41] Under the Hawthorne effect diminishing over time patients as well as their physicians respond differently when informed that BP control and/or medication taking would be carefully evaluated. It may provide an explanation why in the reviewed trials BP improved over time even on constant medications regimens, and why in two RCTs of moderate quality sole ECMDs use failed to demonstrate additional benefit to BP values. All of these mean sufficient evidence is lacking that CMGM with modern ECMDs providing everyday automated monitoring of dosage execution improves BP control.

CMGM as a component of complex interventions

In two trials of sophisticated design with ECMDs use, augmented in some treatment arms by patient diaries, home BP monitoring or education, positive influence of the device use on BP was recorded. However, short duration and low quality of these trials did not permit us to attribute the results to real specific effects of CMGM and generated an unsolvable problem of differentiation of the effects of

the device alone, the device and feedbacks or additional components of intervention, and, finally, the Hawthorne effect just discussed.

In two RCTs of moderate quality pill counts addicted by telephone-based compliance feedback between patients to a surrogate representative of their physicians were able to improve BP control compared with advanced UC or pure educational mail intervention. Thus, some evidence exists that regular follow-up and supervising of hypertensive patients can be effectively implemented in the form of CMGM with use of telecommunication services. The key features of such services seem to be ability to provide easy and regular patient-physician interaction with necessity for a patient to report personally his (her) real activities.

CMGM in integrated care environment

In two US-based RCTs of the highest quality used a CMGM component incorporated in sophisticated integrated care with an active role of pharmacists statistically and clinically significant improvement of BP levels was reached. Surprisingly, the only one European RCT incorporating an ECMD in the CMGM process with participation of clinical pharmacists failed to demonstrate similar result. It might occur at least partly due to inherent problems in the study design based on the assumption of priority of compliance improvement over pharmacological regimens optimization.

In any case, transferability of the kinds of pharmaceutical care or integrated care tested to other clinical practices outside and even inside the country of origin is very questionable, as it assumes availability and acceptance of qualified clinical pharmacists in the health care sector. To separate the impact of CMGM from other services (customized blister packs or active suggestions to physicians for treatment regimens optimization) in these results is not possible. Moreover, selected implementation of any components based on the trial results would be methodologically wrong, as it is completely unknown which components were

essential and which ones were ancillary. In these trials such complex interventions, while effective, represent undesirable silos and seem to be neither cost effective nor practical in implementation for highly prevalent chronic conditions such as hypertension. Integrated care is a novel concept which should be tested further according to general principles of the health technology assessment.[18] If we consider patient compliance (adherence) as a complex result of interactions between the patient, the physician and the health care system,[13] multifaceted plans for hypertension control deserve consideration. However, the effective components of such plans and their priorities must be identified in a systematic fashion.

CMGM in hierarchy of interventions for hypertension management improvement

Our review provided more insight in establishing priorities of interventions for stepped care approaches of hypertension management which claimed in previous reviews.[16,17] Trials included in this review and dealing with electronic compliance monitoring were predominantly designed on the basis of hypothesis that lack of patient compliance is wide-spread, easily measurable and correctable with ECMDs; hence the last may be the first priority in attempts to improve BP control in previously unsuccessfully treated subjects; and after that drug administration regimens changes should be considered[32,42]. Empirical evidence for this management algorithm has not been obtained. Instead, there was no advantage of ECMDs introduced according to the paradigm mentioned above versus approaches based on initial medication scheme optimization, provided it is made according to the modern evidence-based guidelines and especially along with introduction of modern drugs combinations based on the renin-angiotensin system antagonists with prolonged 24 hour action. Such medications, frequently called as «forgiving drugs» for their ability to preserve BP control in case of an occasionally missed dose[43], represent simple, applicable and effective approach to improve BP levels and control rates, which makes electronic compliance monitoring (including the feedback to

patients via audiovisual reminding) unavailing, at least in some populations. Moreover, attempts to increase compliance with non-optimal treatment regimens with an ECMD in the RCT by Wetzels *et al*[36] was successful, but naturally resulted in not superior BP levels and control rates compared with UC. There are also theoretical grounds against «initial efforts for compliance changes» concept. First, problems in prescribing among physicians are not less common then problems in compliance among patients; it is especially true for drug treatment in hypertension often suffering form therapeutic inertia, requiring rational drug combinations and dosage adjustments[8]. Second, non-adherence to medication regimens in subjects regularly applying for medical services and all the more so participating in trials with compliance control may be not so pronounced as one in general population of hypertensives[19].

Indeed, in general, in the trials reviewed the level of patient compliance was quite high and stable, but in favour of IGs. It is not always translated into hemodynamic benefits, as noted also by others.[15,16] It should be pointed out that the rate of compliance *per se* is neither an aim of management nor a surrogate guarantee of better treatment results[16]. Its precise relationships with different outcomes of disease management (including hard clinical endpoints, important surrogate measures, organizational outcomes, costs, etc.) should still be evaluated comprehensively. That is why we are not concentrated in the review on compliance numbers as outcomes.

The role of different CMGM components

We did not find any definite evidence that CMGM with ECMDs use is superior in influence on any hypertension management outcomes compared with other compliance measures. In contrast, the patterns of feedbacks provided during CMGM programs seem to be of greater importance for treatment results. In trials with ECMDs use alone transmission of compliance data for treating physicians and

their discussions with patients were quite rare; these circumstances might affect the study results. The option of reminding to patients themselves incorporated in some modern ECMDs seems to have no sound effect. The central figure in the feedback processes should be the treating physician; however, it was revealed that different mediators (a nurse, an automatic call machine) recognized by the patient as the ambassador of his (her) doctor can reasonably increase the frequency of contacts and hence may be used effectively. These conclusions based on the available empirical evidence strictly correspond to the modern paradigm of patient compliance (adherence), assuming regular interaction of patient and physician on the matter in the process of treatment, in concordance with their initial agreement[13].

The role of populations

Other predictors of trial results may be related to populations studied. CMGM is a complex behavioural process and patient characteristics also need to be considered. The studies were concentrated on a quite narrow pool of mild-to-moderate hypertensive patients making generalization of conclusions to important groups of patients like ones with severe or complicated hypertension impossible. Higher BP levels at study entry could result in greater treatment effects than lower values, which may be subject to the so-called «floor effect» whereby only small further reductions are possible. Similar logics may be applied for compliance initial levels and changes, when we may anticipate more pronounced BP changes in case lower initial levels of compliance forwarding its marked improvement during CMGM.

Non-hemodynamic outcomes of CMGM

The quantity and quality of the information regarding the influence of CMGM on outcomes other then hemodynamic ones are scarce. Up to date there is modest evidence that complex interventions incorporating CMGM component might be accompanied by increase in drug regimen changes in certain cases, but this

relationship seems to be not casual. We can suppose that telecommunication-based CMGM with pill counts use is acceptable for patients and cost-effective, but it requires further evaluation.

Almost nothing is known about patient satisfaction with ECMDs, but high dropouts of patients in some trials can indirectly indicate the problems of such kind. Another concern is feasibility of ECMDs in routine clinical practice, hence frequent attempts in designs of the evaluated studies to perform short-term and/or selective electronic compliance monitoring could mask the real effectiveness of the intervention.

Limitations of the study

A major concern to our review was the insufficient quality of existing trials. Any proposed future trials need to address the major design weaknesses highlighted in this review. The most important requirements to be fulfilled in future trials are need to be suitably powered to detect meaningful (clinically significant not just statistically significant) differences between arms, robust randomization, confounding addressed, ensuring adequate allocation concealment and blinding procedures when possible. Patient attrition must be not only adequately reported, but dealt with in any final intention-to-treat analyses.

Other limitations of our study are generated from the limited scope of trials included. To create a comprehensive health technology assessment of CMGM not only BP changes must be considered, but also other clinically important hard endpoints and surrogate outcomes like end-organ damages, patients' health-related quality of life and preferences, as well as economic and organizational outcomes. It should be pointed out that clinical, economic and patient-centered outcomes may be influenced in different directions.[44] Unfortunately, up to date patient-related outcomes and economic ones are practically of scope of available studies of CMGM in hypertension.

Opportunities for generalization of the results of the systematic review for different health care systems and settings are not yet available. It is known that behavioural patterns in physician-patient interrelationships are diverse in different socio-cultural contexts. For example, patients in Eastern European countries usually tend to highly paternalistic relations with physicians on medication issues, whereas Western Europeans typically welcome cooperation.[45,46] Hence, they may substantially differ in their attitudes to various CMGM approaches.

Finally, as only published studies were retrieved for this review, the finding may potentially overestimate the benefits of CMGM.

Implications for future CMGM research

The previous comprehensive reviews on patient compliance matters have applied quite strict criteria of study selection and based mainly or exclusively on RCTs.[15-17] Taking into account the results of the previous works as well as the new scope of the problem, we intentionally expanded the inclusion criteria to explore grey areas of research, to draw directions and to make suggestions for designs of future investigations. We were convinced that CMGM research is ongoing and promising. However, they should be not only intensified, but, first of all, undergo prompt methodological changes.

First, future studies should be thoroughly controlled for ongoing antihypertensive treatment confounding and incorporate currently agreed standards for pharmacological treatment of patients with hypertension. Further research could only be approved if CMGM is used in concordance with up-to-date high quality clinical guidelines for hypertension management. This argument also predetermined the scope and the time horizon of the current review.

Second, RCTs of high methodological standards with comparison of different complex approaches (preferably composed of two or three distinguishable components) for hypertension management improvement are of the highest priority.

Third, efforts for study planning and performing with evaluation of CMGM programs should be based on both ECMDs and other compliance measures (pill counts, pharmacy refill records, etc.) as each method of measuring compliance has its own strengths and limitations. Such studies should be concentrated on critical patient groups: elderly, subjects with multiple chronic disorders and/or with multiple drug regimens, with complicated and/or severe hypertension, other persons with pre-revealed problems regarding compliance with medications.

Forth, further research should be concentrated on effectiveness of comprehensive CMGM approaches incorporating all pre-specified components: compliance monitoring *per se* as a basic component, different models of feedback to the treating physicians, and counselling, with special attention to their frequency and possible combination with interactive psychological and behavioural procedures.

Fifth, the evolution of the techniques of CMGM with ECMDs use should be addressed, as well as general progress in telemedicine, permitting novel opportunities for feedback via more sophisticated computer feedback equipment with use of personal smartphones and mobile computers.

Hypertension is a lifetime disease and requires long-term pharmacological interventions which predetermine implementation of reliable and permanent supporting measures. Though there is a little wisdom to anticipate that the infrastructure of such measures must be rigid for years, trials of longer duration need to demonstrate true effectiveness of CMGM. Such trials would need to address the existence and importance of the Hawthorne effect and the «white coat» effect; to avoid the last one the use of ABPM and/or home BP self-monitoring would be welcomed. Meantime, the useful information might be generated also from creation,

support and analysis of large, well-designed databases (registries) of hypertension management in different health care settings.

Conclusions

In this review devoted solely and comprehensively to immediate compliance management as a health technology, but not as a surrogate measurement tool, no sound evidence was revealed that CMGM with ECMDs use as a sole intervention has a specific influence on BP control in hypertension treatment. Limited short-term positive effects on BP and no long-term benefits of CMGM as a component of complex interventions were demonstrated. No studies were performed on influence of CMGM on mortality, morbidity, hypertension target organ damages as well as patient-reported outcomes and organization of care (with exception of drug regimens changes).

Regarding the importance of different components of CMGM, regular feedback to the treating physician, but not to the patent himself seems to be essential. It may be realized via telecommunication and with participation of the physician's "ambassador" (a nurse, a pharmacist). Such intermediate caregivers can increase the frequency of necessary feedbacks and intensify simultaneously the counselling component of CMGM.

Pharmacological regimens optimization according to contemporary well-prepared clinical guidelines, alongside with other quality improvement interventions, should precede any efforts on patient compliance management. Introduction of modern once daily preparations in the drug treatment plan may abolish the necessity of implementation of CMGM programs in mild-to-moderate hypertension.

Although there may be other reasons to the use of this technology, we found no convincing evidence for the effectiveness of any particular CMGM approaches to make sound recommendations for their incorporation in hypertension management. This does not, however, mean the evidence of absence of CMGM effectiveness in view of non-optimal study designs and their methodological quality. Any future research needs to be conducted using accepted quality standards and given contemporary guidelines for the treatment of hypertension, especially in relation of medication choice and prescribing. Such studies should be concentrated on specific

groups of patients with compliance problems. To be considered as a useful and applicable health technology in the modern armamentarium of hypertension management in a particular healthcare setting not only hemodynamics but other outcomes of CMGM should be considered and tested in appropriate context including economic, patient-reported (quality of life, preferences and satisfaction) and organizational ones.

References

1. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005: 353: 487-497.
2. Horwitz RI, Horwitz SM. Adherence to treatment and health outcomes. *Arch Intern Med* 1993; 153: 1863-1868.
3. Hodgson TA, Cai L. Medical care expenditures for hypertension, its complications, and its comorbidities. *Med Care* 2001; 39: 599-615.
4. Simpson SH et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 2006; 333 (7557): 15. DOI: 10.1136/bmj.38875.675486.55
5. Kearney PM et al. Global burden of hypertension. *Lancet* 2005; 365: 217-23.
6. Psaty BM et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 2003; 289: 2534-2544.
7. Burnier M. Blood pressure control and the implementation of guidelines in clinical practice: can we fill the gap? *J Hypertens* 2002; 20:1251-1253.
8. Redon J et al. Practical solutions to the challenges of uncontrolled hypertension: a white paper. *J Hypertens* 2008; 26 (Suppl. 4): S1–S14.
9. Ong KL et al. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension* 2007; 49: 69-75.
10. Wolf-Maier K et al. Hypertension treatment and control in five European countries, Canada, and the United States *Hypertension* 2004; 43: 10-17.
11. Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. *Am J Hypertens* 2006; 19: 1190-1196.
12. Vrijens B et al. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ* 2008; 336: 1114-1117.
13. National Institute for Health and Clinical Excellence. *Medicines adherence: involving patients in decisions about prescribed medicines and supporting*

adherence. NICE Clin Guideline 76, January 2009. http://www.nice.org.uk/CG76 (accessed 30 December 2010).

14. Hughes D. When drugs don't work: Economic assessment of enhancing compliance with interventions supported by electronic monitoring devices. *Pharmacoeconomics* 2007; 25(8): 621-635.
15. Schroeder K et al. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. *Cochrane Database of Systematic Reviews* 2004: Issue 3: Art. No.: CD004804. DOI: 10.1002/14651858.CD004804.
16. Haynes RB et al. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD000011. DOI:10.1002/14651858.CD000011.pub3.
17. Glynn LG et al. Interventions used to improve control of blood pressure in patients with hypertension. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD005182. DOI: 10.1002/14651858.CD005182.pub4.
18. Carter BL et al. The potency of team-based care interventions for hypertension: a meta analysis. Arch Intern Med 2009; 169(19): 1748-1755.
19. Wetzels GE et al. Facts and fiction of poor compliance as a cause of inadequate blood pressure control: a systematic review. *J Hypertens* 2004; 22:1849–1855.
20. Christensen A. et al. Electronic monitoring of patient adherence to oral antihypertensive medical treatment: a systematic review. *J Hypertens* 2009; 27:1540-1551.
21. World Health Organization. *Adherence to long-term therapies. Evidence for action.* Geneva, World Health Organization, 2003. http://www.who.int/chp/knowledge/publications/adherence_introduction.pdf (accessed December 30, 2010).
22. Hawkshead J, Krousel-Wood MA. Techniques for measuring medication adherence in hypertensive patients in outpatient settings: advantages and limitations. *Dis Management Health Outcomes* 2007; 15 (2): 109-118.

23. Walsh JM et al. Quality improvement strategies for hypertension management: a systematic review. *Med Care*. 2006; 44(7): 646-657.
24. Khan K et al. *Undertaking systematic reviews of research on effectiveness. CRD's guidance for carrying out or commissioning reviews.* CRD Report Number 4 (2nd ed.). York, UK: Centre for Reviews and Dissemination, University of York, 2001.
25. Higgins JPT, Altman DG, eds. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009 www.cochrane-handbook.org (accessed 30 December 2010).
26. Walker N et al. Standards for CHERG reviews of intervention effects on child survival. *Int J Epid* 2010; 39:121-131.
27. Moher D et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med* 2009; 151: 264-269.
28. McKenney JM et al. Impact of an electronic medication compliance aid on long-term blood pressure control. *J Clin Pharmacol* 1992; 32: 277-283.
29. Friedman RH et al. A telecommunications system for monitoring and counseling patients with hypertension: impact on medication adherence and blood pressure control. *Am J Hypertens* 1996; 9: 285-292.
30. Waeber B et al. Improved blood pressure control by monitoring compliance with antihypertensive therapy. *Int J Clin Pract* 1999; 53: 37-8.
31. Bertholet N et al. Why objective monitoring of compliance is important in the management of hypertension. *J Clin Hypertens (Greenwich)* 2000; 2: 258-262.
32. Burnier M et al. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. *J Hypertens* 2001; 19: 335–341.
33. Marquez Contreras E et al. Efficacy of telephone and mail intervention in patient compliance with antihypertensive drugs in hypertension. ETECUM-HTA study. *Blood Pressure* 2005; 14: 151-158.

34. Lee JK et al. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA* 2006; 296: 2563-2571.
35. Mengden T et al. Management of patients with uncontrolled arterial hypertension: the role of electronic compliance monitoring, 24-h ambulatory blood pressure monitoring and candesartan/HCT. *BMC Cardiovasc Disord* 2006; 6: 36.
36. Wetzels GE et al. Electronic monitoring of adherence as a tool to improve blood pressure control. A randomized controlled trial. *Am J Hypertens* 2007; 20:119–125.
37. Carter BL et al. A cluster randomized trial to evaluate physician/pharmacist collaboration to improve blood pressure control. *J Clin Hypertens (Greenwich)* 2008; 10: 260-271.
38. Santschi V et al. Impact of electronic monitoring of drug adherence on blood pressure control in primary care: a cluster 12-month randomised controlled study. *Eur J Intern Med* 2008; 19: 427–434.
39. Christensen A et al. The impact of an electronic monitoring and reminder device on patient compliance with antihypertensive therapy: a randomized controlled trial. *J Hypertens* 2010; 28: 194-200.
40. Braunholtz DA et al. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epid* 2001; 54:217-224.
41. McCarney R et al. The Hawthorne effect: a randomised, controlled trial. *BMC Med Res Methodol* 2007; **7**: 30. DOI:10.1186/1471-2288-7-30.
42. Burnie M et al. Monitoring compliance in resistant hypertension: an important step in patient management. *J Hypertens* 2003; 21(Suppl.2): S37-S42.
43. Palatini P et al. Maintenance of blood-pressure-lowering effect following a missed dose of aliskiren, irbesartan or ramipril: results of a randomized, double-blind study. *J Hum Hypertens* 2010; 24: 93-103.

44. Kozma CM et al. Economic, clinical, and humanistic outcomes: a planning model for pharmacoeconomic research. *Clin Ther* 1993; 15:1121-32.
45. Naik AD et al. Improving hypertension control in diabetes mellitus: the effects of collaborative and proactive health communication. *Circulation* 2008; 117: 1361-68.
46. Pechère J-C et al. Non-compliance with antibiotic therapy for acute community infections: a global survey. *Int J Antimictrob Agents* 2007; 29: 245-253.

Appendices

APPENDIX 1. PICOS paradigm of the systematic review

Population	adult patients with verified essential hypertension
Intervention	patient compliance management (measurement, feedback, counselling) i.e. compliance measurement-guided medication management (CMGM)
Comparators	comparison with no compliance management intervention ("usual care"); or comparison of different techniques of compliance measurement / management among themselves (different CMGM components)
Outcomes	any, including - clinical (blood pressure, morbidity, mortality) - organizational (managerial) - patient-reported (humanistic) - economic
Study design	randomized controlled trials (RCT) (patient-randomized, cluster-randomized, quasi-randomized trials); cohort studies with or without controls (matched, unmatched, historic or internal)

APPENDIX 2. MEDLINE search strategy

Database: Ovid MEDLINE(R) <1950 to July Week 3 2010>

1 exp hypertension/ (184961)
2 blood pressure.ti. (37406)
3 hypertens$.ti. (132155)
4 or/1-3 (230673)
5 exp patient compliance/ (40602)
6 (patient$ adj7 (complian$ or non?complian$)).tw. (16304)
7 (patient$ adj7 (adher$ or non?adher$)).tw. (8443)
8 (patient$ adj7 (persistan$ or non?persistan$)).tw. (78)
9 or/5-8 (56013)
10 exp questionnaires/ (219586)
11 (patient$ adj7 interview$).tw. (19447)
12 Morisky.tw. (95)
13 self-report$.tw. (52545)
14 pill count$.tw. (407)
15 ((pharmacy adj7 refill$) or (pharmacy adj7 claim$)).tw. (795)
16 (biological marker$ or biomarker$).tw. (41232)
17 (electronic adj3 device$).tw. (1979)
18 (electronic adj3 monitor$).tw. (1480)
19 medication$ event$ monitor$ system$.tw. (171)
20 intelligent drug$ administration$ system$.tw. (1)
21 or/10-20 (316290)
22 exp counseling/ (27539)
23 exp feedback/ (34150)
24 exp patient care team/ (45628)
25 counsel$.tw. (51070)
26 feedback$.tw. (56041)

27 ((nurse$ or pharmac$) adj3 (led$ or manage$ or program$ or based)).tw. (21901)

28 exp reminder systems/ (1545)

29 remind$.tw. (7935)

30 or/22-29 (210983)

31 clinical trial.pt. (463526)

32 randomi#ed controlled trial.pt. (295296)

33 epidemiologic studies/ (4814)

34 evaluation studies/ (137461)

35 comparative study/ (1493859)

36 feasibility studies/ (29901)

37 intervention studies/ (4493)

38 program evaluation/ (35669)

39 epidemiologic research design/ (1378)

40 (randomi#ed or controlled or intervention$ or evaluation$ or impact$ or effectiveness or stud$ or comparative or feasibility or program$ or design$).ti. (1738420)

41 or/31-40 (3358091)

42 animal/ not human/ (3427443)

43 41 not 42 (2740402)

44 (editorial or comment or letter).pt. (1013225)

45 21 or 30 (512454)

46 9 and 45 (11084)

47 4 and 46 (609)

48 47 and 43 (320)

49 48 not 44 (319)

50 limit 49 to yr="1980 -Current" (311)

APPENDIX 3. Data extraction form

<table>
<tr><td colspan="4">GENERAL INFORMATION</td></tr>
<tr><td colspan="4">Date of data extraction</td></tr>
<tr><td colspan="4">Reviewer ID</td></tr>
<tr><td rowspan="3">Study ID</td><td colspan="3">Author(s)</td></tr>
<tr><td colspan="3">Article title</td></tr>
<tr><td colspan="3">Publication source: journal / year / volume / pages</td></tr>
<tr><td colspan="4">Country (geographical area) of origin</td></tr>
<tr><td colspan="4">Institutional affiliation(s)</td></tr>
<tr><td colspan="4">Contact address</td></tr>
<tr><td colspan="4">Sponsorships / conflict of interests</td></tr>
<tr><td colspan="4">SPECIFIC INFORMATION</td></tr>
<tr><td rowspan="7">Verification of study eligibility</td><td colspan="3">Correct population Yes/No</td></tr>
<tr><td colspan="3">Correct intervention(s) Yes/No</td></tr>
<tr><td colspan="3">Correct outcome(s) Yes/No</td></tr>
<tr><td rowspan="5">Study design</td><td colspan="2">RCT / manner of randomization</td></tr>
<tr><td colspan="2">Cohort study with matched concurrent controls</td></tr>
<tr><td colspan="2">Cohort study with unmatched concurrent controls</td></tr>
<tr><td colspan="2">Cohort study with historic controls</td></tr>
<tr><td colspan="2">Cohort study with internal controls (before-after study)</td></tr>
</table>

		Other
Population		
Inclusion criteria		
Exclusion criteria		
Recruitment procedures used/ participation rates		
Allocation concealment Yes/No/Unclear		
Characteristics of participants at intervention commencement	Intervention group(s)	Control group(s)
Age		
Gender		
Ethnicity		
Education		
Habituation		
Socioeconomic status/occupation		
Other available details		
Number		

<table>
<tr><td colspan="3">Were intervention and control groups comparable? Yes/No/Partially - specify</td></tr>
<tr><td colspan="3">Disease</td></tr>
<tr><td colspan="3">Duration of hypertension</td></tr>
<tr><td colspan="3">Severity – mild / moderate / severe</td></tr>
<tr><td colspan="3">Previously treated Yes/No</td></tr>
<tr><td rowspan="3">If treated:</td><td colspan="2">Controlled / uncontrolled (resistant)</td></tr>
<tr><td colspan="2">Previous treatment regimens details (if available)</td></tr>
<tr><td colspan="2">Previous compliance estimation (if available)</td></tr>
<tr><td colspan="3">Description of health care setting</td></tr>
<tr><td colspan="3">Primary / secondary / tertiary care / specialized hypertension units (centers)</td></tr>
<tr><td colspan="3">Qualifications of physicians (if available)</td></tr>
<tr><td colspan="3">Qualifications of allied caregivers (nurses, pharmacists, etc. – if appropriate)</td></tr>
<tr><td colspan="3">Intervention</td></tr>
<tr><td colspan="3">Important details of intervention(s) design and comparator(s)</td></tr>
<tr><td rowspan="3">Nature / focus of CMGM intervention</td><td rowspan="3">Solely compliance management</td><td>Compliance measurement / evaluation only</td></tr>
<tr><td>Compliance measurement / evaluation and feedback to patients</td></tr>
<tr><td>Compliance measurement / evaluation and feedback to caregivers (specify)</td></tr>
</table>

<table>
<tr><td rowspan="4"></td><td rowspan="4">Compliance management as a component of complex interventions</td><td>Compliance measurement / evaluation only</td></tr>
<tr><td>Compliance measurement / evaluation and feedback to patients</td></tr>
<tr><td>Compliance measurement / evaluation and feedback to caregivers (specify)</td></tr>
<tr><td>Other components of complex interventions</td></tr>
<tr><td rowspan="3">Compliance measures</td><td colspan="2">direct / indirect
specify in each study group</td></tr>
<tr><td colspan="2">manner of expression / units</td></tr>
<tr><td colspan="2">provider</td></tr>
<tr><td colspan="3">Duration</td></tr>
<tr><td colspan="3">Frequency and total number of compliance checkpoints (including feedbacks if appropriate)</td></tr>
<tr><td colspan="3">Antihypertensive study medications</td></tr>
<tr><td colspan="3">Medication regimens changed during study – Yes (specify)/No</td></tr>
<tr><td colspan="2">Intervention group(s)</td><td>Control group(s)</td></tr>
<tr><td colspan="2"></td><td></td></tr>
<tr><td colspan="3">Other co-interventions / differences in health care delivering</td></tr>
<tr><td colspan="2">Intervention group(s)</td><td>Control group(s)</td></tr>
<tr><td colspan="2"></td><td></td></tr>
</table>

<table>
<tr><th colspan="5">Outcomes</th></tr>
<tr><td>Nature of pre-specified outcome(s)</td><td colspan="4">Office BP values / BP control rates
Ambulatory (24 hours) BP values / BP control rates
Mortality
Morbidity (specify)
Adverse reactions
Patient-reported (specify)
Organizational (specify)
Economic (specify)</td></tr>
<tr><td colspan="5">Assessor(s): Physician / Nurse / Pharmacist / Other</td></tr>
<tr><td colspan="5">Blinding of assessor(s): Yes/No/Unclear</td></tr>
<tr><td colspan="5">Details of BP measurements</td></tr>
<tr><th colspan="5">Analysis</th></tr>
<tr><td colspan="5">Sample size: calculated / actual, in each arm</td></tr>
<tr><td colspan="5">Follow-up: withdrawals rate, reasons (if specified), in each arm</td></tr>
<tr><td colspan="5">Intention-to-treat analysis: Yes/No/Unclear</td></tr>
<tr><td colspan="5">Statistical techniques used</td></tr>
<tr><td colspan="5">Adjustment for confounding</td></tr>
<tr><th colspan="5">Primary results</th></tr>
<tr><td rowspan="2">Pre-specified outcomes</td><td colspan="2">Intervention group</td><td colspan="2">Control group</td></tr>
<tr><td>Before</td><td>After</td><td>Before</td><td>After</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Statistical significance
Other results
Notes

APPENDIX 4 . Study quality evaluation form

GENERAL INFORMATION	
Date of study evaluation	
Reviewer ID	
Study ID	Author(s)
	Article title
	Publication source: journal / year / volume / pages

Quality criteria	***Comments***
RCT: randomization procedure	Yes / No / Cannot tell If yes: truly randomized / quasi-randomized
RCT: Allocation concealment	Yes / No / Cannot tell
Observational study: controls	Matched / Unmatched / Historic / Internal
Blinding	Masking of outcome assessment: Yes / No / Cannot tell Comments
Eligibility criteria specified	Yes / No / Partially (specify)
Population description	Full / Incomplete (specify)
Disease description	Full / Incomplete (specify) Diagnosis verification Yes / No / Cannot tell

Health care setting description	Full / Incomplete (specify)
Study group(s) systematic difference	In baseline characteristics of patient groups: Yes (specify) / No
	In organization of health care: access to physician's visits, consultations, examinations, and other important features
Intervention(s) description	Full / Incomplete (specify)
Medication regimen description	Full / Incomplete (specify) Differences in medication strategies and regimens by groups
Study duration	
Sample size	Calculated: Yes / No Achieved: Yes / No
Losses to follow-up	More then 80% in final analysis: Yes / No / Unclear Absolute numbers and proportions
Intention-to-treat analysis	Yes / No / Cannot tell
Outcomes description	Full / Incomplete (specify) Selective reporting note

Statistical analysis	Adequate: Yes / No If no, specify critique
	Control for confounding: Yes / No
Estimation for risk of biases	selection bias: Yes / No comments performance bias: Yes / No comments measurement (observer) bias: Yes / No comments attrition bias: Yes / No comments
Other notes	
Overall judgment on study quality	High, moderate, low, very low

APPENDIX 5. Grading system for overall score of methodological quality

(Adapted from [26])

1. ***Scoring system***

   Each study is assigned a single score based on a four-point continuum: "high", "moderate", "low", "very low".

2. ***Score for study design***

   RCTs receive an initial grade of "high", OSs studies receive an initial grade of "low" (in case of large well-designed cohort studies – "moderate").

3. ***Score adjustment***

   After a careful assessment of study methods and execution based on information summarized in the study quality evaluation form, a score should be *downgraded one level* if there are serious questions about validity of results related to

   - sequence generation, allocation concealment, blinding (in case of RCT);
   - incomplete outcome data or selective outcome reporting;
   - other important sources / suspicion of bias: performance bias / Hawthorne effect; attrition bias / loss to follow-up;
   - sample size;
   - inconsistencies with other data sources.

   A score should be *upgraded one level* if the researchers either controlled or accounted for all plausible confounders that would have modified the effect of the intervention on the health outcome.

Thus, a high quality study should be of high design (truly randomized RCT with successful allocation concealment and sufficient pre-calculated sample size or large cohort study with parallel matched controls) with blinding of assessors, follow-up more then 80% of participants, adjusted for confounders and comprehensive description of participants, interventions and outcomes.

APPENDIX 6. Checklist of items to include when reporting a systematic review

(According to the PRISMA Statement [27])

Section/topic	#	*Checklist item*	Reported on page #
TITLE			
Title	1	*Identify the report as a systematic review, meta-analysis, or both.*	Title page
ABSTRACT			
Structured summary	2	*Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.*	i-iv
INTRODUCTION			
Rationale	3	*Describe the rationale for the review in the context of what is already known.*	1
Objectives	4	*Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).*	4-6, Appendix 1

Section/topic	#	*Checklist item*	Reported on page #
METHODS			
Protocol and registration	5	*Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.*	xii
Eligibility criteria	6	*Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.*	4-6, Appendix 1
Information sources	7	*Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.*	6
Search	8	*Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.*	Appendix 2
Study selection	9	*State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).*	7

Section/topic	#	*Checklist item*	Reported on page #
Data collection process	10	*Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.*	7
Data items	11	*List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.*	Appendix 3
Risk of bias in individual studies	12	*Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.*	7-8, Appendix 4,5
Summary measures	13	*State the principal summary measures (e.g., risk ratio, difference in means).*	8
Synthesis of results	14	*Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.*	8
Risk of bias across studies	15	*Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias,*	7-8, Appendix 4,5

Section/topic	#	*Checklist item*	Reported on page #
		selective reporting within studies).	
Additional analyses	16	*Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.*	Not done
RESULTS			
Study selection	17	*Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.*	9-10, Figure 1
Study characteristics	18	*For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.*	9-12, 21, Table I (13-17)
Risk of bias within studies	19	*Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).*	21-23, Table II (18-20)
Results of individual studies	20	*For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.*	23-29, Table III (30-36)

Section/topic	#	*Checklist item*	Reported on page #
Synthesis of results	21	*Present results of each meta-analysis done, including confidence intervals and measures of consistency.*	Not done
Risk of bias across studies	22	*Present results of any assessment of risk of bias across studies (see Item 15).*	21-23
Additional analysis	23	*Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).*	Not done
DISCUSSION			
Summary of evidence	24	*Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).*	37-42
Limitations	25	*Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).*	43-44
Conclusions	26	*Provide a general interpretation of the results in the context of other*	44-48

Section/topic	#	*Checklist item*	Reported on page #
		evidence, and implications for future research.	
FUNDING			
Funding	27	*Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.*	xi