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THEMED ISSUE REVIEW

Scalability of effective adherence interventions for patients using cardiovascular disease medication: A realist synthesis-inspired systematic review

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Upscaling of medication adherence interventions to routine care is still challenging. This realist theory-inspired review aimed to assess which intervention aspects are potentially important for the scalability of effective cardiovascular disease (CVD) medication adherence interventions and how they are reported in effectiveness studies. A total of 4097 articles from four databases were screened of which ultimately 31 studies were included. Relevant information on scalability was extracted using a theoretic framework based on the scalability assessment tool used in the QUALIDEC study for the following domains: (i) innovation, (ii) implementers and patients, (iii) adopting organizations and health system, and (iv) socio-political context. Extracted articles were analysed for themes and chains of inference, which were grouped based on commonality and source of evidence to form new hypotheses. Six different domains relevant for scalability of adherence interventions were identified: (1) Complexity of the intervention; (2) training; (3) customization of the intervention; (4) drivers of the intervention; (5) technical interventions; and (6) stakeholder involvement. These six domains might be useful for the development of more scalable interventions by bridging the gap between research and practice. Data relevant for scalability is not well reported on in effectiveness trials for CVD medication adherence interventions and only limited data on scalability has been published in additional papers. We believe the adoption and reach of effective CVD medication adherence interventions will improve with increased awareness for the necessity of scalability in all phases of intervention development.

KEYWORDS
adherence, cardiovascular, clinical pharmacology, primary care, realist synthesis

1 | INTRODUCTION

Cardiovascular diseases (CVDs) are responsible for the highest mortality rates globally, accountable for an estimated 17.9 million deaths each year.[1] Treatment options include a plethora of medicines such as antihypertensives, cholesterol-lowering drugs and anticoagulants, as well as lifestyle changes, but only half of all CVD patients managed to achieve an adequate level of medication adherence.[2,3] This diminishes treatment effectiveness and increases symptom severity, mortality, hospitalization, healthcare utilization and costs for CVD patients.[4–6] Over the last decades, a multitude of interventions have been developed to improve medication adherence for CVD patients such as technical interventions like medication reminder apps, educational interventions and interventions to increase motivation.[3,7]

Estimates suggest that in general only 14% of all effective interventions are implemented into routine care and their implementation takes on average 17 years[8,9] (see Figure 1). Although no exact figures are known, this also holds true for adherence interventions. This research-to-practice gap can partly be explained by researchers and journals emphasizing internal validity, often at the expense of the contextual factors that make science relevant to practice. Interventions might be successful in improving medication adherence and thereby clinical outcomes in a controlled study environment, but the necessary details to implement the intervention in a real-world setting are often lacking.[10] As a result, despite decades of medication adherence research, non-adherence remains a substantial health problem to date.[11]

Bridging the gap between research and practice requires appraising the scalability of an intervention. Scalability is the ability of an intervention shown to be efficacious on a small scale or under controlled conditions to be expanded under real-world conditions to reach a greater proportion of the eligible population while retaining effectiveness.[12] The successful delivery of complex health interventions at scale requires a close fit between interventions, the sociopolitical contexts and the health systems in which they are implemented.[13] This is a complex challenge, which requires developing, refining and testing implementation strategies that aim to bridge the research-to-practice gap from the start of the project.[14,15] These strategies should be based on an understanding of barriers and facilitators to implementation at scale.[16] However, scalability of an effective medication adherence intervention has often been an "afterthought".[17,18] Consequently, the intervention might be effective in a clinical setting, but might not fit into the real-world healthcare setting, thus hampering scalability.

While there is still a gap between research and practice, in recent years scalability has received increased attention. Theoretical guidance on the concept of scale-up has become increasingly available, and a number of frameworks have been developed that can aid in appraising scalability, planning for scale-up, or both.[17,19,20] These frameworks are largely based on Roger's diffusion of innovation theory and Glaser's formulation of factors related to knowledge transfer.[15,21] A usable scalability framework is the one used by Zamboni et al. in the context of the QUALIDEC study and is based on a synthesis of key factors influencing scale-up emerging from multiple scale-up frameworks[13,22] such as attributes of the intervention, the implementers and the adopting community, supportive organizational culture and leadership and the socio-political context. This framework is designed specifically for a qualitative assessment of intervention scalability in a research setting and consists of a user-friendly questionnaire, rather than a set of theoretical concepts, which aids its application as an analytical framework.

We chose this framework to expand on a recent paper by Zullig et al. that described seven medication adherence interventions for type 2 diabetes patients that have potential for scalability.[10] The aim of the study was to assess which intervention aspects may be important for the scalability of effective CVD medication adherence interventions and how they are reported in effectiveness studies.

2 | METHODS

2.1 | The realist review approach

Appraising scalability requires synthesizing evidence from a broad range of study designs with both quantitative and qualitative data, something traditional systematic review methodology is not designed for. A helpful methodological alternative is the realist review.[23–25] Realist reviews are increasingly more common.[26] In contrast to

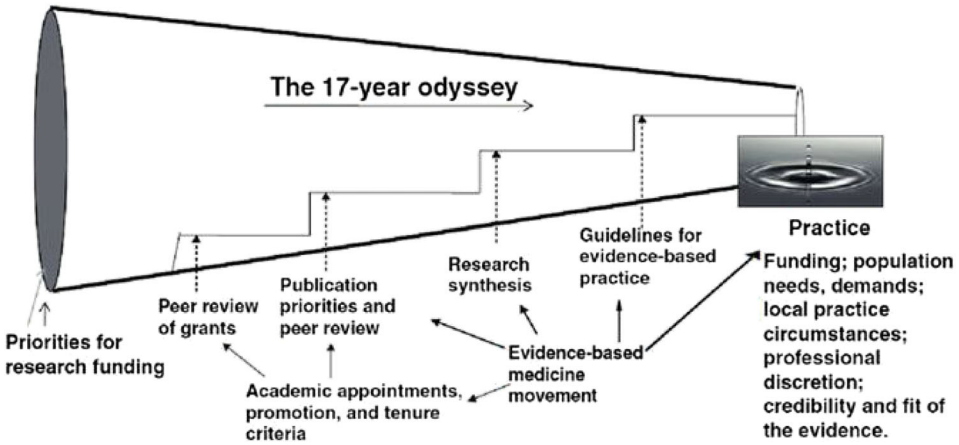

FIGURE 1 The pipeline concept of disseminating research to get evidence-based practice. From Green, L. W. (2008). Making research relevant: if it is an evidence-based practice, where's the practice-based evidence? Family Practice, 25 (Supplement 1), i20–i24. doi:10.1093/fampra/cmn055

traditional data synthesis approaches, realist review uses a theory-driven approach to answer how, why and in what contexts complex interventions may work (or not) by focusing on the relationships between context, mechanisms and outcomes. This review is inspired by the realist review approach and uses the RAMESES publication standards for realist reviews[27] (see Appendix A in the Supporting Information). This approach consists of four methodological steps: (i) defining the scope of the review (concept mining and framework formulation); (ii) searching for and scrutinizing the evidence; (iii) extracting and synthesizing the evidence and (iv) developing the narrative, including hypotheses. Yet, our study deviated from the realist review methodology by using a search strategy and study selection that were driven more by traditional systematic review approaches.

2.2 | Step 1. Defining the scope of the review

The focus of this paper is to assess the scalability of medication adherence interventions in CVD. The scalability assessment framework used in the QUALIDEC study by Zamboni et al.[13,22] was chosen as an initial theoretical framework. The framework consists of the following domains: (1) attributes of the innovation, (2) attributes of the implementers, (3) attributes of the adopting organization and health system, and (4) socio-political context. These four domains were further operationalized to extract relevant data from the included articles. This operationalization was done through consensus discussions by S.H., M.V. and L.v.D. about how to interpret different aspects of the theoretical framework. (See Table 1 for an overview of the theoretical framework and its domains.) Under the first domain attributes of the innovation, evidence strength and quality were considered higher when interventions demonstrated an effect on multiple adherence measurements,[28] when the effect was sustained for a longer follow-up period, or when both an effect on adherence as well as a relevant blood level was found. Relative advantage was defined as the degree to which an innovation is perceived as being better than current usual care in that setting.[15] Adaptability was considered higher when intervention aspects could in theory be altered, for instance by choosing a different interventionist. Trialability was defined as "*the ability to test the intervention on a small scale in the organization, and to be able to reverse course (undo implementation) if warranted*".[15] An intervention was considered more complex when it consisted of more steps or more components. The second domain "Attributes of the implementers" was adjusted to "Attributes of the implementers and patients" as perspectives of patients, being the interventions' target group, are an important aspect of every intervention and its scalability. The scalable unit, under the domain "socio-political context", was defined as a microsystem or a mesosystem that can be replicated as the intervention is scaled up.[19]

2.2.1 | Expert sessions

Two 1-hour expert sessions with three participants each were held to gather feedback on the theoretical framework. Participants were experts in the fields of scalability and/or medication adherence and were asked by e-mail to participate in one of the expert sessions. Selection of participants was done purposively to include a mix of policymakers, researchers and/or practitioners. The online sessions started with a brief presentation (10 min) about the proposed methodology and theoretical framework, after which participants provided feedback and suggestions. These sessions led to some additions to the theoretical framework. The first domain "Attributes of the innovation" was expanded with the two attributes "interventionist" and "mechanism". Interventionist was defined as the primary performer of

TABLE 1 Theoretical framework based on the scalability assessment framework used in the QUALIDEC study by Zamboni et al.[13,22]

Domain	Attributes of the innovation	Attributes of the implementers and patients	Attributes of the adopting organizations and health system	Socio-political context
Operationalization	What are attributes of the intervention that might influence scalability? (interventionist, mechanism, intervention source, evidence strength and quality, relative advantage, adaptability, trialability, complexity, design quality & packaging and costs)	How is the target organization involved by the implementers in the development, execution and evaluation of the intervention?	1) What aspects of the intervention might require additional (ICT) systems, infrastructure or human resources to implement at scale? 2) How similar is the intervention to usual care or other intervention in the setting, or are major departures from institutional norms and values necessary? 3) Were any drivers of the implementation of the intervention identified during the study?	1) Does the policy and legal framework (including financial, economic and procedural incentives) support implementation of the intervention at scale? Is any data available on the further scale-up or maintenance of the intervention? 2) Has a stakeholder analysis been conducted with established mechanisms and time points for continuous engagement of stakeholders after the intervention period? 3) Is the scalable unit clearly defined?

the intervention. Mechanism was defined as the means by which an intervention aimed to achieve better medication adherence. Categories were technical, motivational, educational or a combination. Additionally, the third domain "Attributes of the adopting organization and health system" was expanded with a third question "Were any drivers of the implementation of the intervention identified during the study?" Drivers were defined as stakeholders that are partners with the researchers during the development and testing of the intervention or partnered facilitating parties such as developers of primary care ICT systems, professional societies or policymaking organizations. These organizations were deemed important as they might have an interest in further promoting the uptake of the intervention after the study period. Lastly, experts during the sessions expressed concerns regarding the availability of data in the included studies to properly gauge scalability of an intervention. This led to the additional data collection through interviews or a questionnaire with the corresponding authors of included studies.

2.3 | Step 2. Search for evidence

2.3.1 | Search strategy

The electronic databases PubMed, Embase.com, Web of Science and Cinahl (Ebsco) were systematically searched from inception up to 13 March 2020. The search strategy was developed in collaboration with a clinical librarian and contained the following keywords and MeSH terminology: "cardiovascular drug" AND "Primary Health Care" AND "Medication Adherence" AND "Intervention". The search was performed without language restrictions. A fully detailed version of the search strategy used for all databases is presented in Appendix B in the Supporting Information.

2.3.2 | Eligibility criteria

Interventions were considered for inclusion if: (i) they were (exclusively) intended to promote CVD medication adherence, (ii) they are proven effective on either medication adherence and/or a relevant clinical outcome (i.e., systolic and diastolic blood pressure, total cholesterol, LDL and HDL cholesterol, triglycerides). Only effective studies were considered for inclusion as they were seen as the most promising interventions for further scale-up. The study should be a medication adherence intervention, meaning all studies finding a relevant clinical effect should have achieved this affect through improvements in medication adherence, rather than, for instance, lifestyle changes or medication titration. This means studies describing an intervention consisting of both medication adherence and lifestyle changes or medication titration were excluded if they only showed an improvement in clinical outcomes and no improvement in medication adherence. (iii) Interventions were tested or developed for use in primary care, (iv) with an experimental study design with a control group receiving usual care and (v) a follow-up period of minimally 14 weeks in order to see sustainable effects and (vi) the study was conducted in Europe, the United States, Canada, Australia or New Zealand to promote comparability of healthcare systems.

2.3.3 | Study selection

Articles were screened with the use of the web application for systematic reviews Rayyan[29] and were subsequently evaluated based on their title and abstract by five individual researchers, consisting of two interns (J.S. and B.T.) and three researchers (S.H., M.A. and M.V.). Each title and abstract were evaluated by two researchers and disagreements during this process were resolved through consensus. If consensus was not reached, the article was evaluated again with a third researcher (S.H.). The study was subsequently included or excluded based on the decision of at least two researchers. After the initial selection step, articles were evaluated for eligibility based on their full text by S.H., J.S. and B.T. Disagreement was achieved through consensus, with M.V. being involved if consensus was not reached.

2.3.4 | Manual search for additional papers

After inclusion of the studies, additional publications on the same projects such as a protocol publication, process evaluation or economic evaluation were searched for manually. This was done by using the reference list of the included articles and by using important search terms from the publications such as the names of first and last authors, project names or any other defining characteristics of the studies such as population or setting, as well as common additional publication topics such as "protocol" or "process evaluation". The availability of additional publications is mentioned in Appendix C in the Supporting Information, and any additional information obtained was extracted.

2.3.5 | Additional data collection with questionnaire and interviews

Corresponding authors of all included articles were contacted by e-mail on 7 September 2021 with a request to fill in a questionnaire, or alternatively participate in a brief structured interview lasting approximately 30 minutes. A reminder e-mail was sent out on 3 October 2021. Topics for the questionnaire and interviews were identical, and included questions regarding the implementation of the intervention, recruitment, stakeholder analyses, maintenance of the intervention by healthcare providers after the project had ended, any plans to scale up the intervention and a request for any unpublished work or data on the intervention and its implementation. Questions were constructed to best identify topic areas of the theoretical framework that were not often reported on in the included articles. The

questionnaire/topic list can be found in Appendix D in the Supporting Information. Any additional information provided through either questionnaires or interview was extracted.

2.4 | Step 3. Appraise primary studies and data extraction

2.4.1 | Data extraction

The four domains from the theoretical framework developed in step 1 were used to extract data from all included studies (Table 1). A data extraction table was constructed in which questions from each domain were answered based on both qualitative and quantitative data obtained from the included studies (Appendix C). An indication that the information is not available was given when the field could not be filled in based on the available data.

2.5 | Step 4. Synthesize evidence and drawing conclusions

Data from the extraction table (Appendix C) was synthesized by open coding important themes and by listing chains of inference between the themes.[23,25] This was done in an iterative process by S.H., M.V. and L.v.D. These themes and chains of inference are listed in Appendix E in the Supporting Information. S.H. and M.V. first both analysed a quarter of all included studies for themes and chains of inference independently and resolved any disagreements through consensus discussions to increase validity. Afterwards, all articles were open coded for themes and chains of inference by S.H., M.V. and L.v.D.

Subsequently hypotheses were formed from the chains of inference by cumulatively grouping chains of inference based on commonality. Both the frequency of each hypothesis was listed, as well as listing the source from which the hypothesis was derived. The source could be either the included article from the systematic search, from any additional articles found on the project through the manual search or from additional interviews or questionnaires. Evidence for hypotheses was considered stronger when the hypothesis was found in a higher number of studies, as well as when it was derived from multiple sources. Multiple sources were deemed relevant as it gave the ability to triangulate the data found from multiple sources.

3 | RESULTS

3.1 | Systematic search results

The search strategy resulted in the identification of 4097 potential articles after removal of duplicates (Figure 2). After screening abstract and title, 3837 articles were excluded that did not meet our inclusion criteria. The full text was obtained of 160 studies. After screening these full texts, 31 articles met our criteria and were included for analysis.

3.2 | Characteristics of included studies

An overview of study characteristics of included studies can be found in Table 2. Included studies consisted of intervention studies of which 25 were randomized controlled trials, and seven studies used other quasi-experimental designs such as matched control groups. Medication adherence was most commonly measured with pharmacy refill or claims data ($n = 19$), followed by Medication Event Monitoring Systems (MEMS, $n = 6$). Ten studies included a secondary clinical outcome such as blood pressure or cholesterol level. Included studies were conducted in 10 different countries, with the USA ($n = 16$) being the most prevalent. Most studies ($n = 21$) were led by community pharmacists or pharmacy staff members, six studies had GPs or practice nurses as interventionist and three studies used external interventionists, such as an external organization synchronizing medication. Most interventions used a combination of mechanisms such as motivation and education to achieve better adherence in CVD patients ($n = 14$), followed by educational interventions ($n = 8$) and technical interventions ($n = 5$).

3.3 | Additional data collection by manual search and questionnaires/interviews

The manual search for additional articles publishing results from the same study resulted in an additional 18 articles belonging to 10 of the included studies.[61–77] For the other 22 included studies, no additional publications were found. Additional papers were most commonly process evaluation papers ($n = 5$), followed by protocol papers ($n = 3$) and pilot or pre-studies ($n = 3$). Authors of five studies completed the questionnaire and the authors of five other studies were interviewed (response rate 31%). These interactions also led to the addition of three unpublished works.

3.3.1 | Data extraction based on theoretical framework

Data from included articles as well as information found through the manual search for additional publications and data from interviews and questionnaires were extracted in a data extraction table (see Appendix C in the Supporting Information). Data extraction was informed by the four domains of the theoretical framework. An overview of the availability of data and how it was extracted is presented in Table 3. Data on the first domain, "attributes of the intervention" were well reported and could be extracted from all of the 31 included studies. Data on "attributes of the implementers and patients" were

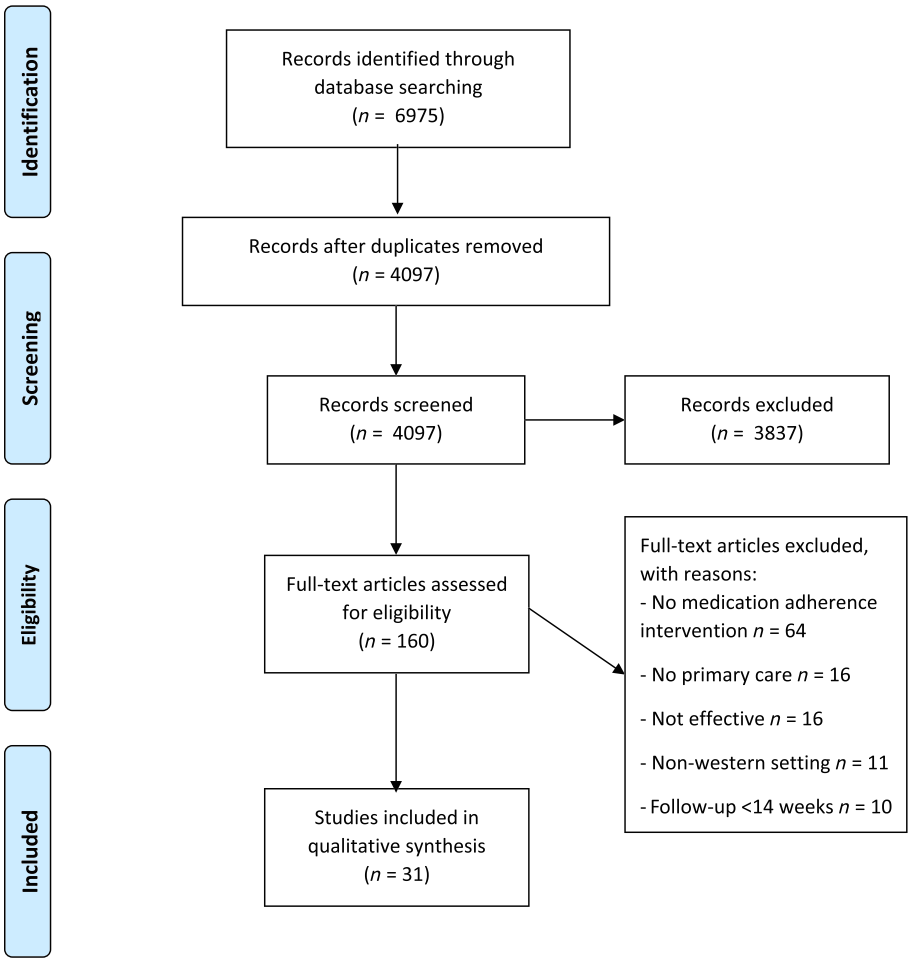

FIGURE 2 Flow diagram of study selection

reported on in eight included studies, and for six included studies this data could be derived from additional publications, interviews and/or questionnaires. Most of these data were evaluations of the study, such as patient or provider satisfaction questionnaires or process evaluations. For 14 studies, data on "attributes of the implementers and patients" were unavailable. Data on "attributes of the adopting organizations and health system", such as the human resources required to carry out the intervention, the comparability with usual care or information about drivers of the intervention were never mentioned directly in the included articles. Therefore, data for this domain was derived indirectly or obtained from additional publications, interviews and/or questionnaires. For example, the human resources required to carry out an intervention could be derived from the time spent on the intervention and a potential driver of the intervention could sometimes be derived from the authors' affiliations or from acknowledgements or funding information. Data for the last domain, the sociopolitical context, was never reported on in the primary included effectiveness trials. Studies never mentioned the policy or legal changes required for scale-up of the intervention, so these data were derived based on common knowledge by the researchers. None of the primary included effectiveness trials mention a stakeholder analysis and none of the primary included effectiveness trials have clearly defined the scalable unit. Lastly, information about the sustainment of the intervention, i.e., whether it was still used by the involved healthcare providers after external funding had ended, was also never reported on in the included studies. Data for this last domain was therefore often extracted from interviews and questionnaires, and in one case extracted from an additional publication on stakeholders' perspectives.

3.4 | Hypotheses about important attributes for the scalability of CVD medication adherence interventions

The chains of inference derived from the data extraction table in Appendix C were grouped based on commonality in Table 4. Following the realistic theory review method, this grouping led to the development of hypotheses about potential important attributes for scalability. For each hypothesis, we report the number of studies that this hypothesis was derived from. Hypotheses are considered to provide stronger evidence when there are more studies that supported the hypothesis, as well as when the hypothesis could be derived from multiple different sources. Hypotheses were subdivided into six categories based on content by the researchers and are described here.

TABLE 2 Characteristics of included studies

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
Abughosh et al.[30] US	186 patients with hypertension and diabetes, nonadherent to ACEIs/ARBs (PDC < 0.8). IG: ($n = 87$) CG: ($n = 99$)	Patients recruited from the Texas-based MAP, United States	The IG received a brief pharmacist phone call intervention to identify adherence barriers, compared to UC in the CG	A pharmacist working at the health plan	Adherence rates to ACEIs/ARBs, as PDC	The intervention lasted 6 months (follow-up at 6 months)	The intervention resulted in significantly better PDCs ($\beta = 0.3182$, $P < .001$). The IG was more adherent based on dichotomous PDC (OR = 3.56, 95% CI = 1.06–11.86)	No clinical outcomes studied
Abughosh et al.[31] US	496 patients on antihypertensive medication. IG: ($n = 248$) CG: ($n = 248$)	Patients recruited from the Texas-based MAP, United States	A two-arm prospective, randomized controlled trial. The intervention group received 6 MI phone calls compared to UC in the control group	11 specially trained pharmacy students on rotation at the MAP	Adherence rates for both the intervention and control groups, as PDC	The intervention lasted 6 months, with monthly follow-up calls	Completing the initial call and ≥ 2 follow-ups was associated with less discontinuation (OR = 0.29; 95% CI = 0.15–0.54; $P < .001$).	No clinical outcomes studied
Abughosh et al.[32] US	152 patients using statins with 304 matched controls	Patients recruited from a Texas based Medicare Advantage prescription drug plan (MAPD).	The intervention was an initial counselling call and up to 2 monthly follow-up calls by pharmacy students trained in MoI, providing education consistent with a previously identified pattern of use	Pharmacy students trained in MoI	PDC, as continuous and dichotomized as PDC ≥ 0.8, as well as discontinuation	The intervention lasted 6 months, with 2 monthly follow-up calls	Mean PDC for the intervention group (0.67 ± 0.3) was significantly higher than the control (0.55 ± 0.4; $P < .001$). The intervention group was less likely to discontinue (OR = 0.38; 95% CI = 0.19–0.76)	No clinical outcomes studied
Blenkinsopp et al.[33] UK	282 hypertensive patients recruited by their community pharmacist. IG: ($n = 167$) CG: ($n = 115$)	Patients recruited from 20 community pharmacies located at a health authority area in England	The IG received a structured, brief questioning protocol to identify medication-related problems	25 community pharmacists	Self-reported adherence (MARS) and prescription refill data and blood pressure control	The intervention lasted 6 months and was delivered three times, at two-month intervals	Adherence rates in the IG increased from 52.3% pre-intervention to 62.9% post-intervention compared to	Patients whose blood pressure was uncontrolled prior to the study were more likely to become controlled in the

TABLE 2 (Continued)

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
			and information needs related to hypertension				51.0% to 50.0% in the CG ($P < .05$)	intervention group (R0.05)
Borah et al.[34] US	21 044; 106 829; and 73 560 patients for antidiabetic, statin, and RAS Antagonist use, respectively, with approximately equal number of intervention and control subjects in each drug class	Members of a large US pharmacy benefits manager (PBM) who did not adhere to prescription	The PBM sent letters to prescribing physicians of nonadherent members, requesting that they discuss adherence barriers and potential solutions with their patients	Prescribing physicians	Both binary (cut-off 80%) and continuous PDC measures	The intervention lasted two years in 2011 and 2012	Physician mailing was associated with 11%, 16%, and 7% higher odds of being adherent by members in antidiabetic, statin, and RAS antagonist cohorts, respectively (all $P < .001$)	No clinical outcomes studied
Bouvy et al.[35] the Netherlands	152 Dutch heart failure patients. IG: ($n = 74$) CG: ($n = 78$)	Patients recruited from 79 community pharmacies in the Netherlands	A pharmacist-led intervention to improve medication compliance. Consisting of a structured interview discussing drug use, reasons for non-compliance and integration of medication into daily life. The CG received UC	Specially trained community pharmacists in the Netherlands	Medication compliance to loop diuretics (MEMS)	The intervention lasted 6 months, with follow-ups on a monthly basis	Over the 6-month study period, patients in the IG had 140/7656 days of non-compliance compared with 337/6196 days in the CG (RR = 0.33, 95% CI: 0.24–0.38).	No clinical outcomes studied
Brennan et al.[36] US	29 247 diabetic patients over forty. IG: ($n = 5123$) CG: ($n = 24\,124$)	Patients recruited from 12 CVS pharmacy benefit management companies in Indiana, US	The intervention included calls from a pharmacist, discussing non-adherence and offering	CVS retail pharmacists that underwent specific training to deliver the intervention	Change in medication adherence rates defined as total days' supply per month	The intervention lasted 18 months, with follow-ups every 6 months	Patients in the IG had an additional 0.75 (2.1%) days' supply/month during the period of the intervention	No clinical outcomes studied

(Continues)

TABLE 2 (Continued)

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
			prescription refills, as well as in-store consultations when picking up prescriptions. The CG received UC.				compared to patients in the CG ($P < .01$, 95% CI: 1.0–3.3)	
Casebeer et al.[37] UK	551 participants on lipid-lowering medication IG: ($n = 355$) CG: ($n = 196$)	Patients recruited from physician's office in 39 different states	Controlled trial	Education program and counselling	Adherence to filling statin prescriptions	The intervention lasted 120 days	Patients in IG achieved a 12.4 higher average number of statin prescription fill days and were 10% more likely to fill prescriptions for at least 120 days ($P = .01$)	No clinical outcomes studied
Doshi et al.[38] USA	1.357 patients on lipid-lowering medication or antidiabetic agents IG: ($n = 679$) CG: ($n = 678$)	Patients recruited from the Humana MAP D plan in the US	Quasi-experimental study	Phone consultation with a pharmacist	Medication adherence based on PDC	The intervention lasted 12 months	Statistically significant absolute increases in mean PDC for lipid-lowering medication (+0.04) and for antidiabetic medication (+0.05)	No clinical outcomes studied
Eussen et al.[39] the Netherlands	899 patients on statin medication IG: ($n = 439$) CG: ($n = 460$)	Patients recruited from 26 community pharmacies in the Netherlands	Open-label randomized controlled trial	5 individual counselling sessions by a pharmacist	Adherence to statin adherence in terms of discontinuation of treatment	The intervention lasted 1 year, where dispensing records were collected at the end of follow-up	Patients in IG had a significantly lower rate of discontinuation versus CG (HR 0.66, 95% CI 0.46 to 0.96)	No clinical outcomes studied
Holdford & Inocencio[40] USA	10.060 patients receiving ≥2 refills for chronic medication	Patients recruited from rural pharmacies in the	Quasi-experimental study	Appointment-based medication synchronization program	1-year adherence rates based on PDC	The intervention lasted 4 months (June 30, 2011	Mean PDCs for the control group ranged from 0.58 to 0.63, while	No clinical outcomes studied

TABLE 2 (Continued)

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
	IG: ($n = 5.030$) CG: ($n = 5.030$)	Midwestern United States				and October 31, 2012)	those for patients in the appointment-based medication synchronization program ranged from 0.80 to 0.87. The difference was statistically significant for each drug class	
Hovland et al.[41] Norway	1.480 patients on cardiovascular medicines IG: ($n = 726$) CG: ($n = 754$)	Patients recruited from 67 Norwegian pharmacies	Unblinded randomized controlled trial	2 consultations with a pharmacist	Self-reported adherence measured by the MMAS-8	The intervention lasted 9 months (October 2014 till June 2015)	88.7% of the patients in the IG were adherent after 18 weeks vs. 83.7% in the CG (5.0% difference, 95% CI 0.8–9.2, $P = .021$)	No clinical outcomes studied
Kardas[42] Poland	198 outpatients with untreated hyperlipidaemia	General practice	Open-label, prospective, randomized study	Educational counselling at each visit (that is every 8 weeks)	Medication possession ratio (MPR)	48 weeks	Mean ± SD MPR was 95.4 ± 53.7% and 81.7 ± 31.0%, for intervention and control group, respectively ($P < .05$)	No clinical outcomes studied
Kooij et al.[43] the Netherlands	6.721 patients on treatment with RAS-inhibitors and statins IG: ($n = 3.094$) CG: ($n = 3.627$)	Patients recruited from 53 community pharmacies in the Netherlands	Pragmatic cluster randomized trial	Telephone counselling by pharmacists	Refill adherence measured over 1 year expressed as dichotomous outcome (refill rate ≥ 80%)	The intervention lasted 1 year	More patients starting with RAS-inhibitors had a refill ratio ≥80% in the IG compared to CG (81.4 vs. 74.9% with OR 1.43, 95%CI 1.11–1.99)	No clinical outcomes studied
Lee et al.[44] US	200 elderly patients	Walter Reed Army Medical Center	A multiphase, prospective study	Standardized medication	Proportion of pills taken vs baseline,	12 months (of which 6 months	The persistence of medication	Significant reductions in systolic BP in the

(Continues)

TABLE 2 (Continued)

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
			with an observational phase and a randomized controlled trial	education, regular follow-up by pharmacists, and medications dispensed in time specific packs	secondary outcomes associated changes in LDL-C and BP.	randomization phase)	adherence decreased to 69.1% (16.4%) among those patients assigned to usual care, whereas it was sustained at 95.5% (7.7%) in pharmacy care ($P < .001$)	pharmacy care group (−6.9 mm Hg; 95% CI, −10.7 to −3.1 mm hg) *vs* the usual care group (−1.0 mmHg;95% CI, −5.9 to 3.9 mmHg; $P = .04$)
Murray et al.[45] US	314 low-income patients, 50 years or older, with heart failure. IG: ($n = 122$) CG: ($n = 192$)	Patients recruited from Indiana university medical group, Indianapolis	The pharmacist assessed patient knowledge and provided the IG with education and instructions about proper medication use. The CG received UC	An intervention pharmacist trained by an interdisciplinary team of investigators	Medication adherence (MEMS) and total direct costs	The intervention lasted 9 months, with follow-up visits every 3 months	During the intervention, medication adherence was 67.9% in the CG group and 78.8% in the IG (10.9 percentage points difference [95% CI: 5.0 to 16.7])	No clinical outcomes studied
Nguyen et al.[46] Australia	120 patients on ACE inhibitors, statins or hypoglycaemic medication IG: ($n = 60$) CG: ($n = 60$)	Patients recruited from 2 community pharmacies in Australia	Prospective randomized trial	Tailored intervention by pharmacist	Difference in the mean medication adherence questionnaire (MAQ) score at 3 and 6 months	This study lasted 6 months, with follow-up at 3 and 6 months	Statistically significant improvement in adherence in the IG compared to CG at 3 months (mean MAQ score 0.42: 95% CI (0.27 to 0.57) *vs* 1.58: 95% CI (1.42 to 1.75); $P < .001$). The IG MAQs compared to CG was sustained at 6 months (0.48: 95% CI (0.31 to 0.65) *vs* 1.48: 95% CI (1.27 to 1.69); $P < .001$)	No clinical outcomes studied

TABLE 2 (Continued)

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
Ogedegbe et al.[47] US	190 African-American patients with hypertension. IG: ($n = 95$) CG: ($n = 95$)	Patients recruited from 2 community-based primary care practices in New York City, US	Patients in the IG followed a MI program, receiving behavioural counselling about medication adherence, compared to UC in the CG	Trained research assistants using a structured MI counselling script	Medication adherence (MEMS) and within-patient change in blood pressure	The intervention lasted 12 months, with follow-up visits every 3 months	Adherence rates in the CG decreased throughout the study period from 55.2% at baseline to 42.9%. Adherence rates in the IG remained stable (from 55.4% at baseline to 56.9%; $P = .027$).	The between-group difference in systolic and diastolic BP was −6.1 mm Hg ($P = .065$) and −1.4 mm Hg ($P = .465$), respectively, in favour of the MINT group.
Park et al.[48]US	563 Advantage Part D (MAPD) beneficiaries with hypertension in each of the intervention and control groups	Medication therapy management call centre	Quasi-experimental design comparing the change in medication adherence between the intervention and matched control groups	Live interactive conversation with patients to assess the use of their medications	Medication adherence (PDC)	6 month pre-intervention with 6 months follow-up	Mean PDC (standard deviation) increased significantly during postintervention period by 17.3% (33.6; $P < .001$) and 13.8% (32.3; $P < .001$)	No clinical outcomes studied
Patel et al.[49] Australia	623 patients on antiplatelet, statin or ≥2 blood pressure lowering medication IG: ($n = 311$) CG: ($n = 312$)	Patients recruited 33 general practices in Australia	Prospective randomized open-label trial	Polypill-based intervention	Self-reported use of indicated combination treatment at study end	The study lasted for 24 months and follow-up was measured at 12 and 24 months	At study end, 70.1% of participants in the IG reported use of combination treatment, compared with 46.9% of the CG (RR) 1.49; 95% CI 1.30 to 1.72; $P < .0001$)	No significant differences were found on systolic blood pressure or total cholesterol

(Continues)

TABLE 2 (Continued)

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
Pladevall et al.[50] Spain	877 patients >50 years of age with uncontrolled hypertension	Physicians from hospital-based hypertension clinics and primary care centers across Spain	Cluster-randomized trial	Counted patients' pills, designated a family member to support adherence behaviour, and provided educational information to patients	Primary outcome was blood pressure control at 6 months, secondary outcome medication adherence	Mean follow-up of 39 months	Intervention patients were more likely to be adherent (odds ratio 1.91, 95% confidence interval 1.19 to 3.05)	Intervention patients were less likely to have an uncontrolled systolic blood pressure (odds ratio 0.62, 95% confidence interval 0.50 to 0.78)
Pringle et al.[51] US	59 496 patients on 1 of 5 different medication classes IG: ($n = 29\,042$) CG: ($n = 30\,454$)	Patients recruited from 578 pharmacists in the USA	Quasi-experimental study	Pharmacy-based intervention via 2 instruments	Medication adherence based on PDC	Interventions lasted 12 months	The mean adherence rates for the five medication classes increased among the IG as compared to the CG	No clinical outcomes studied
Ruppar[52] US	Fifteen adults 60 years old, or older taking at least 1 antihypertensive medication	Senior centres, senior living facilities, and churches and by referrals from health care providers in 2 Midwestern US cities	Pilot randomized controlled trial	Nurse delivered 8-week behavioural feedback intervention	Medication adherence using electronic monitoring	29 weeks	The treatment group had better antihypertensive MA than did the control group (median MA: 100% *vs* 27.3%, $U = 5.00$, $P = .013$).	Systolic BP improved slightly in the intervention group during the study and was significantly different at week 12 (median systolic BP: 130 *vs* 152 mm Hg; $U = 4.50$, $P = .008$).
Schneider et al.[53] US	85 individuals 65 years of age or older being treated with lisinopril for hypertension	Three ambulatory care clinics in the US	Randomized controlled trial	Daily-dose blister packaging (pill calendar) compared with medications packaged in bottles of loose tablets	Prescription refill regularity and medication possession ratio (MPR).	6 months	Intervention group refilled their prescriptions on time more often ($P = .01$) and had higher MPRs ($P = .04$)	Intervention group had lower diastolic blood pressure ($P = .01$)

TABLE 2 (Continued)

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
Schulz et al.[54] Germany	110 patients randomized into the pharmacy care and 127 into the usual care group	9 community pharmacies in nine different Federal States of Germany	Randomized controlled trial	Medication review followed by regular dose dispensing and counselling	Medication adherence as proportion of days covered (PDC)	365 days	Increase in mean adherence to three heart failure medications for 365 days [adjusted difference 5.7%, 95% confidence interval (CI) 1.6–9.8, $P = .007$]	No clinical outcomes studied
Selak et al.[55] New Zealand	513 patients on antiplatelet, statin or ≥2 blood pressure lowering medication IG: ($n = 256$) CG: ($n = 257$)	Patients recruited from 54 general practices in Australia	Open-label randomized controlled trial	Fixed dose combination treatment	Self-reported adherence	The intervention lasted more than 3 years, minimum follow-up was at 12 months	Adherence to all four recommended drugs was greater among IG than CG at 12 months (81% *vs* 46%; RR 1.75, 95% CI 1.52 to 2.03, $P < .001$)	No significant differences in systolic blood pressure, diastolic blood pressure and LDL cholesterol were found
Stewart et al.[56] Australia	Adults with primary hypertension who obtained antihypertensives in the previous 6 months ($n = 395$; intervention $= 207$; control).	Community pharmacy	Cluster randomized controlled trial	Package comprising BP monitor; training on BP self-monitoring; motivational interviewing; medication use review; prescription refill reminders.	Self-reported adherence	6 months	The proportion of patients who were non-adherent at baseline and adherent at 6 months was 22.6% (95%CI 5.1–40.0%) higher in the intervention group (61.8% *vs* 39.2%, $P =$ 0,007).	The mean reduction in systolic BP was significantly greater in the intervention group (10.0 mmHg *vs*. 4_6 mmHg; $P = 0.05$)

(Continues)

TABLE 2 (Continued)

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
Stuurman-Bieze et al.[57] the Netherlands	1002 patients on lipid-lowering medication IG: ($n = 500$) CG: ($n = 502$)	Patients recruited from nine Dutch community pharmacies	Intervention study with a historical control group	Proactive pharmaceutical care intervention programme	Discontinuation rates and non-adherence	The intervention lasted 1 year	After initiation of lipid-lowering drugs, 130 (25.9%) patients in CG discontinued therapy, compared with 68 (13.6%) patients in the IG ($P < .001$); 38 (7.6%) CG patients and 16 (3.2%) IG patients continued use but were nonadherent ($P = .003$)	No clinical outcomes studied
Vollmer et al.[58] US	21 752 patients on cardiovascular medication interactive voice recognition call (IG): ($n = 7247$) interactive voice recognition call+ (IG): ($n = 7250$) CG: ($n = 7255$)	Patients recruited from three large maintenance organizations	Parallel pragmatic clinical randomized controlled trial	Regular and enhanced interactive voice response intervention	Medication adherence based on PDC	The intervention lasted 1 year with a 1-year follow-up	Both interventions significantly increased adherence to statins and ACEIs/ARBs compared with CG (1.6 to 3.7 percent-age points)	Among statin users, interactive voice recognition call+ participants had significantly lower low-density lipoprotein (LDL) levels at follow-up compared with UC ($\Delta = -1.5$; 95% CI, −2.7 to −0.2 mg/dL); this effect was seen mainly in those with baseline LDL levels >100 mg/dL ($\Delta = -3.6$; 95% CI, −5.9 to −1.3 mg/dL).

TABLE 2 (Continued)

Author, country	Study population	Setting	Design	Interventionist	Outcomes	Duration and follow-up	Effect on medication adherence	Effect on clinical outcomes
Vrijens et al.[59] Belgium	392 patients on statin IG: ($n = 194$) CG: ($n = 198$)	Patients recruited from 35 pharmacies from both linguistic regions in Belgium	Randomized controlled trial	Supportive pharmaceutical care program	Post-baseline adherence based on PDC with a MEMS record	The intervention lasted 12 months with a follow-up every month or every 3 months	The intervention resulted in a 6.5% increase in post-baseline adherence ($P < .001$) mainly driven by a 13% increase in persistence at 1 year ($P < .002$)	No clinical outcomes studied
Yeung et al.[60] US	68 primary care patients prescribed targeted heart failure, hypertension, and diabetes medications	County health system in Dallas, Texas	Prospective, matched, quasi-experimental design	Low health literacy medication and disease specific flashcards	Modified Pharmacy Quality Alliance proportion of days covered (PDC) calculation	180 days	At 180 days after intervention, patients in the intervention group had higher PDCs compared with their matched controls (71% vs. 44%; $P < 0.0069$)	No clinical outcomes studied

ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, BP: blood pressure, BMQ: brief medication questionnaire, CG: control group, CVS: consumer value stores, IG: intervention group, MA: medication adherence, MAP: Medicare Advantage Plan, MAQ: Mean Medication Adherence Questionnaire, MARS: Medication Adherence Report Scale, MASES: medication adherence self-efficacy scale, MEMS: Medication Event Monitoring Systems, MI: motivational interviewing, MMAS-4: 4-item Morisky Medication Adherence Scale, MMAS-8: 8-item Morisky Medication Adherence, MPC: mean percentage adherence, MPR: medication possession ratio, PDC: proportion of days covered, RAS: renin-angiotensin system, UC: usual care.

TABLE 3 Availability of data for all included articles based on the theoretic framework and information on how this data was extracted

Theoretic framework domain	Variable	For how many articles was this data present? (included articles $n = 31$)	How was the data extracted? (cited directly, derived based on definition, derived based on common knowledge researcher)
Attributes of the innovation	Interventionist	31	Cited directly
	Mechanism	31	Cited directly
	Intervention source	21	Cited directly
	Evidence strength and quality	31	Cited directly
	Relative advantage	31	Derived based on definition
	Adaptability	31	Derived based on common knowledge
	Trialability	31	Derived based on definition
	Complexity	31	Derived based on definition
	Design quality & packaging*	1	Cited directly
	Costs	9	Cited directly
Attributes of the implementers and patients	How is the target organization involved by the implementers in the development, execution and evaluation of the intervention?	8	Cited directly
Attributes of the adopting organizations and health system	What aspects of the intervention might require additional (ICT) systems, infrastructure or human resources to implement at scale?	31	Derived based on common knowledge
	How similar is the intervention to usual care or other interventions in the setting, or are major departure from institutional norms and values necessary?	31	Derived based on common knowledge
	Were any drivers of the implementation of the intervention identified during the study?	6	Cited directly
Socio-political context	Does the policy and legal framework (including financial, economic and procedural incentives) support implementation of the intervention at scale?	31	Derived based on common knowledge
	Is any data available on the further scale-up or sustainment of the intervention?	10	Cited directly
	Has a stakeholder analysis been conducted with established mechanisms and time points for continuous engagement of stakeholders after the intervention period?	10	Cited directly
	Is the scalable unit clearly defined?	0	Not applicable

3.4.1 | Complexity of the intervention

Four hypotheses were derived related to aspects of the intervention. Less complex interventions are often more scalable. That is because these simpler interventions are often easier to apply to different settings and require fewer human resources. However, this can come at a cost of overall less relative advantage over usual care. More complex interventions often consist of more frequent or intense consultations with healthcare providers, which increases the human resources required and relative advantage compared to usual care. The relationship between complexity and scalability can therefore be seen as a trade-off; interventions that showed higher evidence in their studies were often more complex and therefore less scalable, but might achieve better results when scale is achieved, albeit at a higher cost.

TABLE 4 Hypotheses formulated about scalability of effective medication adherence interventions based on chains of inference found in included articles including the source(s) of the hypotheses

Links of chains of inference	Number of studies that supported this hypothesis	From what source(s) is the hypothesis derived?		
		Included studies	Additional publication	Interview/ questionnaire
Complexity of the intervention				
Lower complexity of the intervention tends to lead to higher adaptability and trialability. The relationship works both ways (i.e., higher complexity leads to lower trialability and adaptability).	18	X	X	X
More complex interventions tend to require more human resources and therefore need a more substantial financial incentive or reimbursement. This relationship works both ways (i.e., less complex leads to fewer human resources).	16	X	X	X
More complex interventions tend to achieve a higher relative advantage. This relationship works both ways (i.e., lower complexity leads to lower relative advantage).	16	X	X	X
The use of intervention components that are further from usual care (e.g., pharmacy students as interventionist, motivational interviewing for pharmacy staff members) may limit the scalability	6	X		X
Training				
An extensive training for interventionists to be able to perform the intervention may limit the trialability of the intervention	5	X		X
A more extensive training might be necessary for implementation when the intervention consists of components not similar to usual care	2	X		X
Customization of the intervention				
Intervention tailored to patients (e.g., past adherence trajectory) improves the relative advantage of the intervention	12	X	X	X
Basing or adapting the intervention on preferences of patients and/or HCPs, a pilot study or previously proven methods increases the satisfaction with the intervention	4	X	X	X
Drivers of the intervention				
A driver of the intervention, i.e., an organization with an interest to further scale-up the intervention after the study period has ended, was involved when an intervention became usual care	6			X
A driver of the intervention might improve the sustainability of an intervention by keeping materials such as ICT applications or measurement tools available after the study period has ended.	2			X
Technical interventions				
Interventions that are technical in nature tend to require very limited human resources and therefore little financial incentives, but rather require ICT, legal or policy changes	5	X	X	
Interventions that are technical in nature tend to be not trialable, due to substantial changes required in ICT and/or legal or policy changes required	4	X		

(Continues)

TABLE 4 (Continued)

Links of chains of inference	Number of studies that supported this hypothesis	From what source(s) is the hypothesis derived?		
		Included studies	Additional publication	Interview/ questionnaire
A full integration of the intervention in existing ICT systems promotes maintenance of the intervention	4			X
Stakeholder involvement				
A stakeholder analysis after the intervention has been evaluated in a trial promotes possible scale up, by identifying both strengths and limitations of the innovation in different settings	3	X		X
Proven cost-effectiveness or application of an intervention into usual care elsewhere may improve the chances of further scale-up of an intervention	3			X

Additionally, more complex interventions often consisted of aspects further from usual care such as a pharmacy intern as interventionist. This is likely done to lower the costs of the study, but does limit the scalability as these aspects are not present in all target healthcare settings.

3.4.2 | Training

Two hypotheses were derived related to the training for an intervention. Extensive training might make an intervention less trialable, which therefore limits scalability. That is because training itself requires resources. The more extensive the training is, the more resources are required as entry to participate in the intervention. However, sufficient training for healthcare professionals (HCPs) also has a positive effect on the implementation of an intervention, and might be required when the intervention consists of aspects not similar to usual care or requires skills that go beyond usual care. This training might therefore be necessary for the initial implementation during the trial phase of the intervention, but has a negative influence on scalability afterwards.

3.4.3 | Customization of the intervention

Two hypotheses were derived related to the customization of the intervention. The targeting of the intervention to specific patient populations positively influences the relative advantage of an intervention, and therefore the scalability. An example is an intervention that targets solely patients that are currently non-adherent, or focuses on patients starting with new medication. This customization ensures that patients that do not benefit from the intervention are not included and therefore makes the intervention more efficient. Likewise, customization of the intervention to the needs and wishes of the involved HCPs increases the satisfaction with the intervention.

3.4.4 | Drivers of the intervention

Two hypotheses relate to drivers of the intervention. Drivers of the intervention, such as umbrella or policymaking organizations or professional societies, seem to play an important role in potential scale-up. These organizations can be considered important partners from which the developers of the interventions should gather support. Additionally, in some cases these organizations might be important funding organizations or might have paid for intervention materials, which can ensure the intervention is sustained after the initial research funding has ended.

3.4.5 | Technical interventions

Three hypotheses are derived related to technical interventions. Examples of technical interventions, as opposed to interventions that rely on consultations to increase knowledge or motivation, are medication synchronization or electronical reminders for patients. They are often simple interventions that require limited human resources, but instead require legal, policy or ICT changes. This makes the initial implementation harder, but at the same time increases the scalability and sustainability of the intervention once these initial barriers are overcome. These systemic changes can be seen as a one-time investment that HCPs outside of the initial trial location might also benefit from. A related downside is that these interventions sometimes rely on specific ICT systems, which makes these interventions inaccessible for users of different systems.

3.4.6 | Stakeholder involvement

Two hypotheses relate to stakeholder involvement. Stakeholders play an important role in scalability and should ideally be involved from the start. Data such as strengths and limitations of the intervention in a

specific setting, data on (cost-)effectiveness and data about the use of the intervention in different settings are very relevant data for stakeholders and should be gathered during the trial phase and afterwards. Conducting stakeholder analyses from an early phase ensures that the right data is being gathered to pursue stakeholders in further promoting the intervention after the trial phase.

4 | DISCUSSION

Our review was able to find 31 interventions for CVD patients that were effective in improving medication adherence, a relevant clinical outcome, making use of a systematic search. Despite being effective, the majority of these 31 interventions are not routinely used in usual care, and therefore do not contribute to better medication adherence. From these 31 interventions we were able to derive six attributes of interventions that are important for scalability of CVD medication adherence interventions: (1) complexity of the intervention; (2) training; (3) customization of the intervention; (4) drivers of the intervention; (5) technical interventions; and (6) stakeholder involvement.

Less complex interventions can be considered more scalable, but that can come at a cost of overall less relative advantage over usual care. An explanation is that more complex interventions often require coordination among multiple staff members, are strongly dependent on factors within the organizational context such as administrative support, local champions and fit with organizational procedures and programmes.[78] In comparison, simple interventions are less dependent on factors within the organizational context and rely more on the continuing of financial incentives and individual motivation, which might be easier to achieve at scale.

The second attribute found is that an extensive training lowers the scalability of an intervention. Adequate training might ensure the intervention is conducted with high fidelity, but might also lower the trialability of an intervention, which is an important aspect of scalability.[13] If a stakeholder, healthcare organization or another new adopting organization has to decide whether they would like to try out a new intervention on a small scale, a multiple day training for healthcare providers might be a considerable time and resource investment. Therefore, investing heavily in extensive training solely to try out a new intervention might be a too substantial precondition that limits trialability.

The third attribute is that customizing the intervention to HCPs and the target population may lead to better scalability of CVD medication adherence interventions. This is in line with the consensus in the field of medication adherence research that interventions that are tailored to the type and cause of non-adherence and the specific needs of the patients are preferable.[79] Moreover, assessing acceptability among providers and the target population is an important aspect in different frameworks planning for scale-up and might serve as an important input for stakeholders.[17,19,20,80]

Drivers of the intervention are important for scalability, as they might continue to support the intervention after the initial project has ended. This finding is in line with research in different settings, as Shelton et al. showed that interventions are 80% more sustained in settings with external organizational support.[81] Data about drivers of the interventions were never mentioned in the articles themselves, so had to be derived from funding statements and acknowledgements or additional interviews and questionnaires. Despite not being able to confirm the importance of drivers of the intervention from the included papers, interview and questionnaire data did show that each intervention that became usual care in their respective healthcare setting was heavily supported by a driver of the intervention.

Technical interventions to increase medication adherence for CVD patients tend to be more scalable once initial barriers have been overcome. These barriers are often policy, legal or ICT changes, which tend to change at a system level on a larger scale than the initial target setting. Moreover, technical interventions tend to be simple and require fewer human resources, increasing their scalability. This is consistent with previous research on sustainability, which found that new procedures or technologies are more likely to be sustained after the project had ended once fully implemented.[78]

The last attribute is that gathering relevant data for stakeholders increases the scalability of an intervention. Other than being effective in a clinical setting, the intervention needs to be a viable choice for the organization or the setting in which it is delivered.[80] Authors can convince stakeholders of the viability of their intervention at a larger scale by gathering relevant data. Analytic tools such as systematic reviews or economic evaluations can be helpful to increase the speed of uptake of an intervention.[82]

The paper by Zullig et al. describes medication adherence interventions for type 2 diabetes patients that can be considered scalable.[10] We found that most interventions are designed without considering attributes relevant for scalability, which is in line with their finding that most medication adherence interventions are tested without consideration of reach, resources or costs. Another finding was that less complex interventions are more scalable, and likely to be less costly due to fewer human resources being required. The paper by Zullig et al. also suggests making interventions less costly in order to increase their scalability. They also coin e-learning interventions as low-cost alternatives, which coincides with our finding that technical interventions tend to require fewer human resources and therefore lower costs. Lastly, this review found that customizing the intervention to providers' and patients' needs and wishes increases scalability, which is in line with their finding that tailoring of the intervention increases scalability as it reduces costs.

Data relevant for the scalability of effective medication adherence interventions is not often reported in effectiveness trials, with the exception of data on the attributes of the intervention. Additional publications from the same project, such as process evaluations, context analyses or economic evaluations, offer additional data that can help to paint a more complete picture on the scalability of an effective CVD medication adherence intervention. These publications often reported on attributes of the implementers and patients and attributes of the adopting organizations and healthcare system. Data to gauge the socio-political context, such as information on stakeholder analyses or policy or legal changes required to scale up an

intervention, were seldom reported on in either effectiveness trials or additional publications. The main aim of an effectiveness study is not to report on the potential scalability of an intervention. However, this gap between research and practice is a well-documented problem in the literature[8,9,83] and researchers are increasingly stimulated by funding agencies to think about the real-world application of their interventions.[84] Effectiveness is only a single step from inception of an intervention to wide scale use of the intervention.[83] As the development and testing of interventions is paid for by public funds and they are eventually designed to be used in real healthcare settings, researchers have an obligation to not only test the effectiveness of their intervention in a clinical setting, but also to investigate the potential for scalability of their interventions in the target healthcare setting. Traditional RCTs are important as they are considered the gold standard for assessing effectiveness due to their high levels of internal validity. However, this high internal validity comes at a cost of external validity.[80] In research and practice, both internal and external validity play a crucial role as they both provide important information not only about effectiveness, but also among which setting, context or conditions an intervention might work. Nonetheless, only 9 out of 31 papers included in this review published additional articles beyond the effectiveness publication, and if they were published, they were often not indexed together or published in the same journal. Despite the increased availability of theoretical guidance for scalability over the last decade,[13,17,19,20] there remains a lack of empirical evidence on what works in what setting. Researchers are encouraged to integrate the potential for scalability in all phases of the innovation, and to publish data relevant for scalability so other researchers can learn from their example, which will eventually increase the reach, adoption and impact of effective interventions.[80]

4.1 | Strengths and limitations

To the best of our knowledge, our article is the first review to explore the scalability of medication adherence intervention for CVD patients. This was done by combining a systematic approach for identifying studies with realist synthesis methods which allowed the inclusion of different study designs and methodologies. Moreover, traditional data synthesis methods in systematic reviews are aimed at producing a weighted average outcome for all included studies. As scalability is a complicated construct, the realist review methodology allowed us to produce new theories and hypotheses about scalability rather than giving a single weighted scalability score for all included studies. Additionally, a theoretical framework specific for scalability was used and both the methodology and findings were refined with the input from experts in the fields of medication adherence and dissemination and implementation science.[13]

A limitation of the study is that despite the theoretical foundation and input from experts, data often had to be derived indirectly from the articles, which was a subjective process. For example, costs of the interventions were seldom mentioned, but could be derived from the time spent by the interventionist. Similarly, the level of adaptation or core components of the intervention were rarely mentioned, but were gauged by the researchers on agreed upon definitions and common sense. The primary researchers were not experienced with realist synthesis. However, they did consult frequently with K.Z., a co-author with experience with realist synthesis. Moreover, data extraction was based on predefined definitions and frameworks, and the double review of papers in our research team minimized the subjectivity of interpretation.

Additionally, for most of the included articles, relevant data on scalability was lacking. This was particularly the case for the last two domains of the theoretical framework, "attributes of the adopting organisations and health system" and "socio-political context". As a result, there might be more domains or hypotheses relevant for scalability of medication adherence interventions for CVD patients that this review has not been able to find. For example, cost-effectiveness plays an important role in scalability, but unfortunately cost-effectiveness analyses are lacking for the majority of the studies, which limits this review's ability to make hypotheses based on cost-effectiveness.

Another limitation is that this review did not include a quality appraisal. Quality appraisals for these studies, such as the Cochrane risk-of-bias tool for randomized trials (RoB2), assesses potential risk of bias for the effectiveness of interventions, whereas the focus of this review was on the scalability of the interventions.[85]

This review focused on interventions conducted in Europe, the United States, Canada, Australia and New Zealand in order to increase the comparability of healthcare systems, and therefore cannot draw any conclusions about scalability in healthcare systems outside of these areas.

Additionally, Dutch authors whose articles were included in the systematic search were more often willing to answer questionnaires and participate in interviews. This is due to the majority of the researchers involved in this review being Dutch. They were often familiar with the authors of Dutch studies, which likely made the latter more willing to participate in interviews or questionnaires. Moreover, the authors of this review are familiar with the Dutch healthcare setting or might be familiar with additional publications from the same project, which allowed them to use more data from included studies conducted in the Netherlands.

5 | CONCLUSIONS

Our realist synthesis-inspired review explored the scalability of effective CVD medication adherence interventions and identified six attributes of interventions relevant for scalability, including the complexity of an intervention, training, customization of the intervention, drivers of the intervention, technical interventions and stakeholder involvement. Data relevant for scalability are often not well reported on in effectiveness trials for CVD medication adherence interventions and only a handful of projects published results relevant for scalability in additional papers. Researchers are encouraged to integrate the potential for scalability in all phases of the intervention, and to publish important results such as attributes of the intervention, the implementers,

patients and adopting healthcare organizations and the socio-political context. We believe the adoption and reach of effective CVD medication adherence interventions will improve with increased awareness for the necessity of scalability in all phases of intervention development.

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COMPETING INTERESTS

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CONTRIBUTORS

All authors contributed to the conception and design of the study, analysis and interpretation of the data. S.H. and L.S. conducted the systematic search. S.H., M.V., K.Z. and L.v.D. conducted the realist synthesis. S.H., M.V. and L.v.D. drafted the first version of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the submitted version.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article (and its supplementary information files).

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SUPPORTING INFORMATION

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