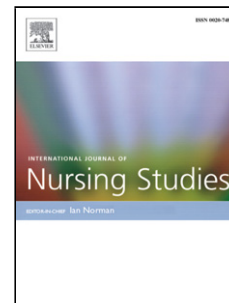# Accepted Manuscript

Title: Clinical and economic outcomes of nurse-led services in the ambulatory care setting: a systematic review

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Title:

Clinical and economic outcomes of nurse-led services in the ambulatory care setting: a systematic review

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Abstract:

Background: With the increasing burden of chronic and age-related diseases, and the rapidly increasing number of patients receiving ambulatory or outpatient-based care, nurse-led services have been suggested as one solution to manage increasing demand on the health system as they aim to reduce waiting times, resources, and costs while maintaining patient safety and enhancing satisfaction.

Objectives: The aims of this review were to assess the clinical effectiveness, economic outcomes and key implementation characteristics of nurse-led services in the ambulatory care setting.

Design: A systematic review was conducted using the standard Cochrane Collaboration methodology and was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data sources: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE EBSCO, CINAHL EBSCO, and PsycINFO Ovid (from inception to April 2016).

Review Methods: Data were extracted and appraisal undertaken. We included randomised controlled trials; quasi-randomised controlled trials; controlled and non-controlled before-and-after studies that compared the effects of nurse-led services in the ambulatory or community care setting with an alternative model of care or standard care.

Results: Twenty-five studies of 180,308 participants were included in this review. Of the 16 studies that measured and reported on health-related quality of life outcomes, the majority of studies (n=13) reported equivocal outcomes; with three studies demonstrating superior outcomes and one demonstrating inferior outcomes in comparison with physician-led and standard care. Nurse-led care demonstrated either equivalent or better outcomes for a number

of outcomes including symptom burden, self-management and behavioural outcomes, disease-specific indicators, satisfaction and perception of quality of life, and health service use. Benefits of nurse-led services remain inconclusive in terms of economic outcomes.

Conclusions: Nurse-led care is a safe and feasible model of care for consideration across a number of ambulatory care settings. With appropriate training and support provided, nurse-led care is able to produce at least equivocal outcomes or at times better outcomes in terms of health-related quality of life compared to physician-led care or standard care for managing chronic conditions. There is a lack of high quality economic evaluations for nurse-led services, which is essential for guiding the decision making of health policy makers. Key factors such as education and qualification of the nurse; self-management support; resources available for the nurse; prescribing capabilities; and evaluation using appropriate outcome should be carefully considered for future planning of nurse-led services.

Highlights

What is already known about the topic?

- Previous systematic reviews showed the effects of nurse-led care were comparable to physician-led care in several settings.
- However, majority of these systematic reviews focussed on single specialty settings, were conducted over 10 years ago, and did not provide a detailed synthesis of economic and process outcomes.

What this paper adds?

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- This paper provides an updated systematic review of the literature, confirming that nurse-led care produce equivalent or better outcomes compared to physician-led/standard care in managing chronic conditions in the ambulatory care setting.

- This paper also suggests a number of important process outcomes such as education and qualification of the nurse; self-management support; resources available for the nurse; and prescribing capabilities. These factors should be carefully considered for future planning of nurse-led services.

- This paper highlights a lack of high quality economic evaluations and provides direction for future economic evaluations of nurse-led services.

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1. Background

With the increasing burden of chronic and age-related diseases, and the rapidly increasing number of patients receiving ambulatory or outpatient-based care, nurse-led clinics or services have been suggested as one solution to manage increasing demand on the health system as they may reduce waiting times, resources, and costs while maintaining patient safety and enhancing satisfaction (1, 2). Nurse-led services developed as an advanced practice role for primary chronic disease management during the 1990s (3). They are now common in a wide variety of clinical and specialist areas and are well established in the USA, UK and Canada in diseases such as: rheumatoid arthritis; diabetes; hypertension; cardiac conditions; musculoskeletal disorders; cancer; and dermatology.

Nurses make up the largest workforce in healthcare and can play a fundamental role in redesigning healthcare models (4). Nurse-led services are complex interventions involving multiple care components (5). They usually follow structured protocols, guidelines and algorithms for decision making and are thus associated with adherence to best practice. They aim to facilitate increased follow-up for patients and improve concordance with guidelines. They are considered to provide safe care, which may result in improved outcomes and potentially lower healthcare costs (6). Commonly, in a nurse-led service, nurses assume their own patient case-loads, work autonomously and manage a patient's health through assessment, monitoring, nursing interventions, and provision of education and support to patients to empower them to manage their own health needs (7). To provide a nurse-led service, nurses generally require educational preparation and training specific to each context of practice. The International Council of Nurses recommends that a Master's degree is required for entry level (8). The nurse-led care model relies on the adept nurse to have the attributes, skills, and

knowledge to competently and comprehensively deliver care (2). Identifying and training such nurses requires careful and considered workforce planning. Policy directives, funding and education opportunities are required to ensure nurses can assume this role and are able to deliver effective and equitable healthcare services (9). One of the most important considerations for a nurse-led service is requirements of appropriate qualifications and ongoing professional development; this underpins a competent service. Careful planning, implementation, accountability and evaluation is required to ensure the service is effective (10).

Several reviews examined nurse-led services for certain health conditions, and suggested these services may be beneficial (11-15). In some settings, studies evaluating substitution of physicians by nurses have found no differences in health outcomes, with some evidence of improved satisfaction (11-15). However, the majority of these reviews are either over 10 years old, focussed on single condition/practice settings or did not include economic and process outcomes as part of the reviews. The focus of this current review was to examine evidence for nurse-led services across all chronic conditions in the ambulatory care setting, where the nurse assumed primary responsibility for patient management and care. Furthermore, this review also synthesised key information regarding implementation of services and examined the economic outcomes of such services.

2. Aims

The primary aim of this review was to assess the clinical effectiveness of nurse-led services in the ambulatory or community care setting. The secondary aims of this review were to examine the economic outcomes and to characterize the nurse-led services by describing (i) the training and qualification requirements of the nurses; (ii) whether self-management support was a component of the nurse-led intervention; (iii) whether the interventions were delivered by nurse

practitioners. These three characteristics were perceived to be critical for informing development of future nurse-led services during the design of this systematic review.

3. Methods

This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was prospectively registered in PROSPERO (ID 42016036924).

3.1. Identification of studies and inclusion criteria

We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library (Issue 4, 2016), MEDLINE EBSCO (1966 to April 2016), CINAHL EBSCO (1982 to April 2016), and PsycINFO Ovid (1967 to April 2016). The searches were restricted to humans and to studies in English. Search terms included combinations of terms to describe the intervention (e.g. nurse-led, nurse practitioners, nurse, nursing) and the setting (e.g. primary care, community, outpatient, ambulatory, clinics) (See Supplementary Material 1). The reference list was also hand searched to further identify relevant studies for inclusion.

Only comparative quantitative evaluative studies were included. Study designs included in this review are: randomised controlled trials; quasi-randomised controlled trials; controlled and non-controlled before-and-after studies. The population of interest were people who received nurse-led services in an ambulatory or community care setting. There was no limitation on diagnosis. Studies that evaluated nurse-led services provided as part of an inpatient service or midwife-led services were excluded. The reviewed interventions were nurse-led services as a model of care where the registered nurse has primary responsibility for patient management

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and care for a cohort of patients located in an ambulatory or community care setting. Studies that used usual care or any other alternative model of care (e.g. physician-led services) as the comparator were included. The primary outcome was health-related quality of life (HRQoL). For the purpose of this review, the authors believed that this was an appropriate primary outcome as it provides a composite measure of issues that are important to a variety of patient populations. The HRQoL measures could be generic or disease-specific as measured by the trial authors. Secondary outcomes included any health-related outcomes including: symptom burden, patient self-management or behavioural outcomes (measured by behavioural uptake), condition-related clinical indicators, patient satisfaction, and health service use such as rates of hospitalisation, emergency presentation, referrals to health services and medication management. In addition, this review also examined economic outcomes and key components and attributes of the nurse-led services.

3.2. Study screening

Two review authors pre-screened all search results (titles and abstracts) for possible inclusion, and those selected by either or both authors were subject to full-text assessment. Two review authors independently assessed the selected articles for inclusion. Discrepancies were resolved by discussion to reach consensus. If a consensus could not be reached, a third review author would have been asked to act as an arbiter. However, this was not required.

3.3. Data extraction

All articles that met the inclusion criteria were included in the review. Data extraction was conducted by two authors. Data extracted included: study methods; authors, publication year, country, study design, characteristics of participants (including age, disease), content and intensity of the interventions, sample size, response rate, outcome measures, intervention

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resources, study results and the level of evidence of the study. Any discrepancies, errors or inconsistencies were resolved by consensus between the two authors through a discussion after reviewing the original article. If a consensus could not be reached, a third review author would have been asked to act as an arbiter. However, this was not required. All studies were classified into non-inferiority or superiority trials as per intended by the trial authors.

3.4. Study quality assessment

Studies were assessed and reported in accordance with the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (16), which recommends the explicit reporting of individual domains including sequence generation for randomisation, allocation concealment, blinding of participants, personnel and outcome assessors (assessed for each main outcome or class of outcome), incomplete outcome data (assessed for each main outcome or class of outcome), selective outcome reporting, and other sources of bias. This led to an overall assessment of the risk of bias of the included studies (17). We assessed each risk of bias item as either low, unclear or a high risk of bias based on the trial reports and/or additional information provided by trial authors.

Two review authors independently assessed the risk of bias in included studies, with any disagreements resolved by discussion to reach consensus. We contacted trial authors for additional information about the study methods as necessary. If a consensus could not be reached, a third review author would have been asked to act as an arbiter. However, this was not required. We incorporated the results of the risk of bias assessment into the review through narrative description and commentary about each item.

3.5. Data synthesis and analysis

Due to the broad inclusion of this review, the included studies contain a large range of study designs (e.g. pre-post, RCT), disease types (e.g. mental illness, cardiovascular), intervention, outcome measures (e.g. clinical outcomes, cost-effectiveness). Therefore, a meta-analysis was considered inappropriate and a narrative synthesis was planned and undertaken.

4. Results

4.1. Search results

A total of 2,863 titles were identified from the initial search. After removing duplicates and screening titles and abstracts, 60 full text articles were retrieved and assessed for eligibility. Of these 60 articles, 25 studies met the inclusion criteria and were included in this review (Figure 1, PRISMA flow diagram).

4.2. Characteristics of the included studies

The 25 included studies involved 180,308 participants and examined nurse-led services in a wide range of conditions and care settings caring for adult patients with heart failure and cardiovascular disease (17-19); asthma (20, 21); aged care (22); dyspepsia (23); post-intensive care(24); pain (25); rheumatology(26, 27); cancer (28, 29); chronic and end-stage kidney disease (30, 31); mental health (32); attention deficit hyperactivity disorder (ADHD) (33), and diabetes/gestational diabetes (34, 35). One study included patients with both human immunodeficiency virus *(*HIV) and severe mental illness (36). Four studies included patients with mixed chronic conditions in the contexts of community health and geriatrics (37-40).

The majority of included studies were conducted in Europe (*n*=15) (18, 20, 21, 23-28, 32-34, 37, 38, 40), with the remaining conducted in Australia (*n*=4) (22, 29, 31, 35), the United States (*n*=3) (19, 36, 39) and Asia (*n*=3) (17, 30). Most were RCTs (*n*=19) (18-21, 23-30, 32, 34, 36,

38-40), with five pre-post studies (17, 22, 31, 35, 37) and one non-randomised controlled trial (33). Of the 19 RCTs, ten were superiority trials (18, 19, 21, 25, 29, 30, 32, 36, 39) and nine were equivalence trials (20, 23, 24, 26-28, 34, 38, 40). The studies had various sizes of samples: >1,000 (*n*=3) (37, 38, 40), between 201 and 1,000 (*n*=10) (17, 19, 22, 24, 29, 32, 34-36, 39), between 101 and 200 (*n*=7) (18, 20, 21, 23, 25, 27, 28), and ≤100 (*n*=5) (26, 30, 31, 33). Characteristics and key findings are illustrated in Table 1.

4.3. Risks of bias of the included studies

The risk of bias assessment for each study is outlined in Table 2. The majority of studies achieved low risk across most domains of assessment (random sequence generation: n=19; allocation concealment: *n*=11; incomplete outcome data reporting: n=17; selective outcome reporting: *n*=11; and other sources of bias: *n*=17). For the six non-RCTs, assessment of risks related to random sequence generation and allocation concealment were not applicable. Due to the nature of nurse-led services, the interventions were not amenable to blinding of participants. Accordingly, all 25 studies were rated as high-risk for this domain of assessment. Blinding of outcome assessment could have been achieved by using data collectors who were blinded to the intervention or objective outcomes such as laboratory markers. However, a total of 11 studies received a high-risk rating for this domain.

4.4. Outcome measures

All outcome measures used by the 25 studies could be categorised into HRQoL (general and disease-specific), symptom burden, self-management and behavioural outcomes, health service/resources use and costs, satisfaction and perception of care, and other clinical indicators (See Table 1). Seventeen studies (68%) measured HRQoL using generic (e.g. SF36, SF12, and EQ5D) or disease-specific HRQoL measures. Symptom burden was assessed in 12 studies

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(48%). Self-management or behavioural outcomes were assessed in five studies (20%). Ten studies measured a range of other clinical indicators related to the specialty (40%). Satisfaction and perception of the quality of care outcomes were measured in 11 studies (44%). Health service/resources use and/or costs were assessed in 16 studies (64%) (see Figure 2).

4.5. Primary outcome

4.5.1. Health related quality of life

Of the 25 included studies, 17 measured HRQoL as an outcome measure for evaluation of the nurse-led intervention (18-26, 28-30, 32-34, 38, 39). One RCT did not report HRQoL results (19). Two studies reported nurse-led interventions improved measures of HRQoL compared to standard care or physician-led interventions (18, 23). One RCT(23) investigated the effects of a nurse-led clinic follow up for dyspeptic patients after direct access gastroscopy and reported improved HRQoL in comparison with GP-led follow up (Mean Difference: MD 140.7, p<0.001). A cluster RCT (n=153) evaluating a nurse-led intervention in addition to standard care designed to improve self-management in patients with heart failure in a primary care setting reported improvements in role function due to physical limitations in comparison with a control group (18).

Most studies (n=13) reported equivocal outcomes in HRQoL between a range of nurse-led care models and standard care (20-22, 24, 25, 27-30, 32, 33, 38, 39). Of these, eight studies (20, 24, 26-28, 32, 33, 38) evaluated nurse-led care compared to physician care in rheumatology (26, 27), respiratory(20), post-cancer surgery follow up (28), mental health(32), ADHD (33), general practice (38) and post-intensive care discharge (24) settings; and five (21, 22, 29, 30,

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39) evaluated the nurse-led care in addition to standard care in the asthma (21), renal (30), chronic disease management(39), post-cancer surgery (29), and dementia care (22) settings.

One RCT (*n*=206) reported patients with type 2 diabetes mellitus receiving care from the nurse-led intervention showed a small but statistically significant reduction in overall physical component scores on the SF36, whereas this did not occur for the group of patients receiving GP led care over the 14 month study period (34).

4.6. Secondary outcomes

4.6.1 Symptom burden

Twelve RCTs showed that there were either no differences (18, 21, 32, 33, 40-42) or significant improvements (23, 26, 27, 30, 39) in symptom burden or resolution of symptoms between those who received care from nurses and from physicians, a multidisciplinary team or standard care.

Seven RCTs (18, 21, 24, 32, 33, 40, 41) found no differences in terms of symptom burden between nurse-led and physician-led (33, 40, 41) or team-based (21) care. These trials were conducted in a range of patient populations including: *acute disease in a primary care setting* such as burns, diarrhoea, back pain, upper respiratory symptoms, urinary discomfort (40); acute asthmatic symptoms (21); ADHD-related symptoms (41), depressive symptoms (18), post-intensive care follow up for depressive symptoms, anxiety and post-traumatic stress (24); and chronic/recurrent major depression or dysthymia (32).

Four trials demonstrated significant benefits or equivalent outcomes in reducing symptom burden using nurse-led care compared to physician-led care (23, 26, 27, 30). A RCT of 175 patients reported a significant difference in the dyspepsia severity score, with patients in the

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nurse-led clinic arm achieving better scores than the GP-led clinic arm (23). Another RCT of 98 patients with end-stage renal failure investigated a nurse-led management program and reported significant improvements in sleep at seven weeks and 13 weeks, and kidney disease related symptoms at seven weeks (the week immediately after the intervention), but not at 13 weeks (30). Two small RCTs (26, 27) of 100 and 107 patients with rheumatology-related conditions reported comparable levels of pain (26, 27) and morning stiffness (26) in both the clinical nurse specialist and physician-led arm.

In addition to the 11 RCTs described in this section, one RCT (39) examined the effects of a nurse-led follow-up intervention compared with usual care on depressive symptoms in social-economically disadvantaged women. This trial reported a significant reduction in depressive symptoms compared to the usual care arm. Control group participants were wait-listed and were offered a reduced form of the intervention when they completed the study (i.e. at the end of their nine month follow-up). The wait-list session included a one-off appointment with the nurse to provide single-appointment case-management services, and Medicaid training

4.6.2 Self-management and behavioural outcomes

Three studies (26, 31, 39) reported significant benefits of the nurse-led services in a range of self-management or behavioural outcomes. A RCT of 432 socio-economically disadvantaged women who received a public health nursing case management intervention had higher levels of Medicaid knowledge and skills competence ($p<0.001$) compared with standard care (39). A small RCT (n=100) that compared the care provided by clinical nurse specialist with care provided by junior hospital doctors for osteoarthritis were comparable in patient self-efficacy

(26). However, patients in the clinical nurse specialist group had better knowledge of managing osteoarthritis (26). Another small before and after study (*n*=52) demonstrated that a series of sessions led by a nephrology nurse practitioner (involving assessment, education, planned medication and life style changes) led to significant improvements in active smoking (*p*=0.003), overall self-management score (*p*<0.001), medication knowledge (*p*<0.001), knowledge of condition (*p*<0.001), healthy lifestyle (*p*<0.005) and medication adherence (*p*=0.044)(31).

One RCT reported no significant difference in diet and fluid non-adherence between patients with end stage kidney disease receiving peritoneal dialysis who received the nurse-led service or standard care (30). One RCT measured the effects of a nurse-led intervention for patients with cardiovascular disease on behavioural outcomes including lifestyle behaviours of dietary intake and physical activity (19). However, the trial did not report on these outcomes.

4.6.3. Condition-related clinical indicators

In total, 10 studies evaluated the effects of nurse-led services compared to physician-led or standard care on a number of other clinical indicators. Five RCTs (21, 27, 29, 34, 38) found no differences between those receiving the nurse-led services and those receiving physician-led/standard care. The populations and outcomes evaluated included GP practice: health status, and compliance of clinical practice guidelines(38); asthma monitoring: lung function test outcomes (FVC1 and PEF) (21); type 2 diabetes mellitus: HbA1c, blood pressure and lipid profile (34); chronic inflammatory arthritis: Disease Activity Score 28, the Health Assessment

Questionnaire (27); post-surgery for colorectal cancer: distress thermometer and supportive care needs (29).

Three RCTs (19, 32, 36) and two before and after studies (31, 35) demonstrated significantly better outcomes in terms of a range of clinical quality indicators. A RCT of 238 people with HIV and mental illness reported that a community-based nurse-led intervention was effective for significantly reducing viral load at 12 months ($p<0.001$) (36). A RCT of 525 patients with documented cardiovascular disease reported an intervention delivered by a nurse practitioner/community health worker team using an individualised treatment regimen based on algorithms improved total cholesterol ($p<0.001$), LDL-C ($p<0.001$), triglycerides ($p=0.013$), systolic blood pressure ($p=0.003$), diastolic blood pressure ($p=0.013$), and HbA1c ($p=0.034$) (19). Another RCT of 558 people with chronic depression in the community setting reported significant improvements in functional impairment in those who received nurse-led regular follow up compared to GP-led care ($p=0.010$) (32).

The remaining two before and after studies were conducted in women with gestational diabetes (n=261) (35) and people with chronic kidney disease ($n=52$) (31). Results from the diabetes study indicated that there was a statistically significant decrease in the number of cases with "neonatal congenital abnormality" ($p<0.0001$) and other adverse neonatal outcomes ($p<0.0001$) after the implementation of the nurse practitioner-led model of care (35). However, there were no significant differences in HbA1c and maternal adverse outcomes. The study of patients with chronic kidney disease (31) involved a series of sessions led by a nephrology nurse practitioner that included assessment, education, planned medication and life style changes). This intervention led to significant improvements in proteinuria ($p=0.002$), eGFR

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(p=0.002), 5-year absolute risk reduction (p=0.002), systolic and diastolic blood pressure (p<0.01 and p<0.001, respectively), cholesterol (p=0.002), and HbA1c (p<0.001) (31).

4.6.4 Satisfaction and perception on the quality of care

Nine RCTs (19, 26, 27, 29, 30, 33, 34, 38, 40) measured satisfaction or perception on the quality of care from the patient's perspective. One RCT (28) reported satisfaction from both the patient's and spouse's perspectives and one study (22) reported satisfaction from the residential aged care facilities management perspective.

In five RCTs (27-29, 33, 38, 40) that compared care delivered by a nurse and a physician/standard care, there were no differences in patient's satisfaction of care. These RCTs included patients with ADHD (33), general community common complaints (38, 40), rheumatoid/inflammatory arthritis (27), and patients requiring post-cancer surgery follow up (28, 29). The two RCTs that were conducted in a post-cancer surgery setting reported no difference in patient satisfaction between nurse-led follow up and standard care (28, 29); however, one trial reported nurse-led follow up resulted in higher spousal satisfaction (p=0.03) (28).

Four RCTs (19, 26, 30, 34) reported patients receiving the nurse-led service were significantly more satisfied or reported higher perceived levels of quality care than those receiving the physician-led service. These RCTs evaluated nurse-led services compared to physician-led services in cardiovascular disease (19), diabetes (34), osteoarthritis (26) and renal care settings (30). The RCT (n=98) that was conducted in patients with end-stage kidney disease reported

nurse-led management significantly improved patient satisfaction at seven weeks (the week immediately after the intervention), but not at 13 weeks (30).

One non-randomised controlled trial (22) reported that a nurse practitioner-led dementia outreach service in residential aged care facilities resulted in significantly higher level of staff satisfaction with regards to dementia care.

4.6.5. Health service use

Hospital admission, length of stay and emergency presentation

Two before and after studies (17, 37) reported nurse-led interventions decreased length of stay, admission rates, and emergency presentations. A controlled before and after study in the UK (n=172,342) compared health service use outcomes of the intervention group (5 practices) with the control group (30 practices) and reported significantly improved rates of unplanned medical and geriatric admissions (p=0.018) and reduced length of stay ≥1 night (p=0.015) (37). Another before and after study (17) reported that a combined home and clinic-based nurse-led intervention for patients with chronic heart failure was effective in shifting inpatient care to outpatient nurse-led care (increased from 5.2±3.2 to 6.4±4.1 times/patient, p<0.001), thereby reducing hospital length of stay (5.3 days, a 26.2% decrement), and hospital admission (36 times, 33% decrement) and emergency presentations (17).

While the two before and after studies (17, 37) reported significant benefits in health service use, seven RCTs (20, 21, 25, 29, 30, 38, 40) showed no differences between nurse-led services and physician-led/surgeon-led/standard care on a range of health service use outcomes. These

trials were conducted in post-cancer surgery (29), pain management (25), asthma (20, 21), general practice (38, 40), and end-stage kidney disease (30) care settings.

Referrals to specialist physicians or allied health services

Three studies (34, 35, 39) reported that nurse-led care resulted in more appropriate referrals to specialist physicians or allied health professionals. A nurse-led care intervention for diabetes showed there were more referrals to an ophthalmologist (p=0.07), referrals to insulin therapy (p=0.015), measures to prevent diabetic foot symptoms (p=0.001), and mean number of visits (p<0.001) (34). Similarly, a before and after study demonstrated that, there was a statistically significant increase in insulin use and referrals to dietitians and diabetes educators, and a significant decrease in referral to physicians for diabetes care, (p<0.0001) after the implementation of the nurse practitioner led model of care (35). A RCT examining a public health nursing case management intervention indicated that women who received the intervention were twice as likely to receive new mental health visits compared to those in the control group (OR=1.92, p<0.007) (39). However, there was no difference in the number of preventive routine care visits (39).

Medication Management

Three RCTs (23, 32, 40) demonstrated varying consultation duration and prescribing patterns between nurses and physicians in their care. A large multicentre RCT of 1,461 participants compared nurses' and physicians' visits for the management of low complexity diseases in the community setting (40). In this trial, the mean visit duration by a general practitioner (GP) was 3 minutes and 6 minutes by nurses (Mean Difference MD =3.195, 95% CI 1.466-4.924). Nurses prescribed drugs in 65.1% of cases, compared to 84.4% prescribed by GPs (Odds Ratio OR: 0.24, 95%CI=0.16, -0.35) (40). Another RCT (n=558) examining practice nurse-led care

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reported a higher number of nurse visits and months in which patients were on anti-depressant medications in the practice nurse group compared to the group receiving GP-led care (*p*=0.026 and 0.047, respectively) (32). For dyspeptic patients, an RCT showed that the nurse practitioner group required significantly less "full dose protein pump inhibitors" use, more "no protein pump inhibitor treatment" compared to those who received GP-led care at 6 months (23). A small before and after study of patients with chronic kidney disease (n=52) demonstrated that a series of sessions led by a nephrology nurse practitioner led to significant improvements in the number of prescribed anti-hypertensives (*p*<0.001), cholesterol lowering medications (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) (*p*=0.003), and aspirin (*p*<0.001) (31).

4.7. Economic outcomes

Five studies included cost analyses (17, 23-25, 28) (Table 3), however, only one was a full cost-effectiveness analysis (24) where costs are considered in relation to health outcomes (Table 3). Four studies were randomised controlled trials (23-25, 28) and one was a pre-post design(17). In a Taiwanese study (17), the nurse-led intervention was the most intensive with 2 weekly home visits initially, plus outpatient visits and telephone calls, but no intervention costs were reported. Other studies had less frequent contact with the nurse (several months apart) and relied on self-help approaches. Hernandez et al. (2014), a superiority trial, concluded the nurse-led intervention was not cost-effective, due to no patient quality of life improvements while costs for inpatient care were higher than the usual care group (24). Health service use costs were lower in the nurse-led interventions compared with usual care for several other studies; €4,004 vs €7,464 (25), €2,592 vs €3,789 (28), post-intervention US$362,722 vs pre-

intervention US\$624,020 (17), £36 vs £72 (23), but these differences were either not statistically significant or statistical approaches did not account for right-skewed cost data. Lower costs were driven by fewer hospital re-admissions, shorter length of stay or less medication use which are overarching goals of nurse-led models of care. However, quality of life measures failed to find significant patient health benefits in three studies (24, 25, 28).

4.8. Key components and attributes of nurse-led services

Three studies explicitly outlined the extensive clinical nursing experience of the nurses involved in the intervention (20, 28) and in the relevant specialty (20, 27, 28). However, none of the included studies specified whether the years of clinical experience or a master's qualification was a requirement for the selection of nurses delivering the intervention. In a number of studies, the nurse delivering the intervention were provided with short, intensive training specific to the practice setting where the nurse-led service was delivered (18, 19, 27, 32, 34, 37). The training was generally delivered by a specialist physician and/or a specialist nurse (18, 27), with varying levels of intensity from hours to weeks (30, 37). The training content included agreed treatment protocols (19), behavioural strategies that improved intervention adherence or behavioural change such as motivational interviewing (19, 32). Many studies did not specify the requirement of Master's qualification except for those interventions that were delivered by nurse practitioners (31, 38).

Over half of the included studies (*n*=13) specifically included self-management as a component of nurse-led care (17, 18, 20, 21, 23, 25, 26, 30-32, 36, 39). Of these studies, only two specified the inclusion of family as part of the self-management intervention (21, 30). In terms of resources available to the nurse delivering the intervention, a number of studies explicitly outlined that the nurse-led service was guided by clinical practice guidelines, protocols or

treatment algorithms (17, 20, 21, 24, 30, 34, 35, 40). In a number of studies, the nurse was provided with a clear referral pathway (40), access to a specialist physician (24, 26, 27) or other allied health professionals (35) as required.

In eight studies (19-23, 31, 35, 38) evaluating nurse practitioner-led care, all nurse practitioners could prescribe or adjust the dosage of medications. In three studies (33, 34, 40), the nurse delivering the intervention were not nurse practitioners but were able to prescribe or adjust medications within an established protocol.

5. Discussion

To the best of our knowledge, this systematic review is the largest review examining the effects of a nurse-led model of care in the ambulatory setting, including 25 original research studies of 180,308 participants. While several reviews exist in the literature (11, 43, 44), this review specifically focussed on studies that examined models of care where registered nurses have the primary responsibilities of care over the patient's condition. Of the 17 studies that reported HRQoL as an outcome measure (18, 20-26, 28-30, 32-34, 38, 39), 13 reported equivocal outcomes (20-22, 24, 25, 27-30, 32, 33, 38, 39), three (18, 23, 30) reported superior outcomes and one (34) reported a small reduction in a single HRQoL domain. Although many of the studies had methodological short-comings in terms of risk of bias, this systematic review affirms findings of previous reviews (43) that appropriately trained nurses can produce high-quality care on par with physicians and achieve comparable health outcomes for patients. Further, no safety concerns were reported by any of the included studies. Of the three studies (27, 35, 40) that measured adverse events, two reported no adverse events (27, 40) and one (35) reported that the cohort receiving nurse-led care had significantly less adverse neonatal events. Therefore, we concluded that nurse-led care is a safe and feasible model of care for

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consideration across several settings. However, it remains unclear whether nurse-led models are cost-saving or cost-effective compared to usual care or alternative models of care such as physician-led care.

Due to the nature of nurse-led services, the interventions were not amenable to blinding of participants and personnel. All 25 studies received a high-risk assessment for this domain of assessment. Blinding of outcome assessment could have been achieved by using data collectors who are blinded to the intervention or objective outcomes such as laboratory markers. Future studies should ensure their study designs eliminate risks of biases in the allocation concealment and selecting outcome reporting domains. It is extremely important for studies to report on all outcomes measured, regardless of direction of results.

Nurse-led services are complex interventions (5) and each component of the intervention requires careful consideration and planning. According to the findings from this review, we propose several key areas for consideration during in the design of future nurse-led models of care and intervention (See Supplementary Material 2). These include documenting: the years of experience in nursing and the specialty; formal qualification and intensive training required for the proposed care population; the appropriateness of clinical privileges such as prescription of medications; whether behavioural change is an objective of the intervention; the use of evidence-based clinical guidelines; the nurse's ability to access a specialist physician and other allied health team members when required.

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With regards to cost effectiveness, the five included studies that measured costs (17, 23-25, 28) cannot answer the question of whether nurse-led interventions had positive economic outcomes. Limitations in these studies included: small samples for assessing differences in costs (17, 23-25, 28), limited scope of cost types considered (e.g. no medication costs for patients with pain (25), no intervention costs considered(17, 23, 28) and incorrect statistical analysis of cost data (17, 23)). One study (24) concluded the nurse-led intervention was not cost-effective, due to no patient quality of life improvements while costs for inpatient care were higher than the usual care group (24). The EQ-5D data collection in this study may not have been collected frequently enough or at the correct intervals or may not have been sensitive to this patient group (24). However, it may also mean the intervention was not of high enough frequency to improve patient outcomes. We recommend that all future trials should include a well-designed economic evaluation or cost-analysis that overcome the abovementioned flaws.

Another challenge is the selection of the right outcomes for assessing the effects of nurse-led services. The outcomes should match the intent of the nurse-led service under testing. It is critical to define what an alternative model of nurse-led care attempts to achieve and to consider the sensitivity and appropriateness of the outcomes measures (37). Given self-management and behavioural change was a key component of the interventions included in 13 studies (17, 18, 20, 21, 23, 25, 26, 30-32, 36, 39), only four studies (26, 30, 31, 39) measured and reported on these self-management or behavioural outcomes. From the findings of this review, we recommend a taxonomy of outcomes for consideration for future service evaluation and research (Supplementary Material 3). These include HRQoL (general and disease-specific), symptom burden, self-management and behavioural outcomes, health service/resources use and costs, satisfaction and perception of care, and other relevant clinical indicators. If there is a detected benefit, it is then important to consider the sustainability of such impact (30). For

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example, patient satisfaction could be transient (30), while patients might be more satisfied with a recent episode of care from the nurse-led clinic, these effects might not necessarily be sustainable after some time (30). Further, given the rising importance of acknowledging the role of family members in supporting the patient in chronic disease management (45), measuring behavioural outcomes and satisfaction of care from the family members' perspective is critical. In this review, only one trial (28) measured satisfaction from the family's perspective.

In terms of educational preparation, this review revealed that the nurses delivering the interventions had extensive clinical experience. Although the International Council of Nurses recommends that a master's qualification should be required for entry-level advanced practice roles (8), there was a lack of (or at least a lack of description of) academic qualification requirements for the nurses delivering the intervention. In countries such as the United Kingdom and Australia, a master's degree is mandatory educational preparation for nurse practitioners. Another issue is the inconsistency and variation of advanced nursing roles or nursing titles used across studies or countries. Although this issue is well acknowledged in the literature (46), this makes comparison of roles across studies difficult. It is also important to note that advanced nursing "roles" or "titles" should not be confused with advanced nursing "practice" (47). In the planning of nurse-led services whereby advanced nursing practice is required, it is essential to ensure the nurse can capably practise across the advanced nursing practice domains including direct care, support of systems, education, research and professional leadership (47).

Nurse prescribing practices are not new, and it is well within the scope of practice of nurse practitioners in many countries to prescribe pharmacotherapies (48). However, there is

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relatively less evidence suggesting the safety and effects of nurse prescribing for non-nurse practitioners. While acknowledging that nurse practitioners could have varying levels of education and preparation depending on the country or setting where they practise, nurses who were not nurse practitioners in three included studies (33, 34, 40) were empowered to prescribe and/or adjust medications. While this review cannot provide a definitive answer as to whether such practice should be encouraged, it is clear that such practices should be supported with appropriate training, the use of evidence-based clinical guidelines and algorithms, and professional standards and legislation.

6. Conclusions

Nurse-led care is a safe and feasible model of care for consideration across a number of settings. With appropriate training and support provided, nurse-led care is able to produce at least equivocal outcomes in terms of patient HRQoL, symptom burden, self-management and disease-specific clinical targets compared to physician-led care for managing chronic conditions. The strategic expansion of community-based nurse-led services has the potential to transform chronic illness care, creating a more accessible, productive and safer healthcare system. However, the potential economic benefits of nurse-led models compared to usual care or alternative models of care such as physician-led care are less certain. High quality health economic evaluations are urgently required to guide the decision making of health policy makers and service planners. It is essential that health administrators and nurse leaders carefully design the components of nurse-led services and measure appropriate outcomes. Future innovations such as prescribing practices of registered nurses should be tested and supported by robust evidence, training, professional standards and legislation.

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Identification

Records identified through database searching (n = 2863)

Additional records identified through other sources (n = 0)

Screening

Records after duplicates removed (n =2281)

Records screened (n = 2281)

Records excluded by title (n = 2221) Records exluded by asbtract

Eligibility

Full-text articles assessed for eligibility (n = 60)

Full-text articles excluded, with reasons (n = 35)

Included

Studies included in qualitative synthesis (n = 25)

Studies included in quantitative synthesis (meta-analysis) (n = 0)
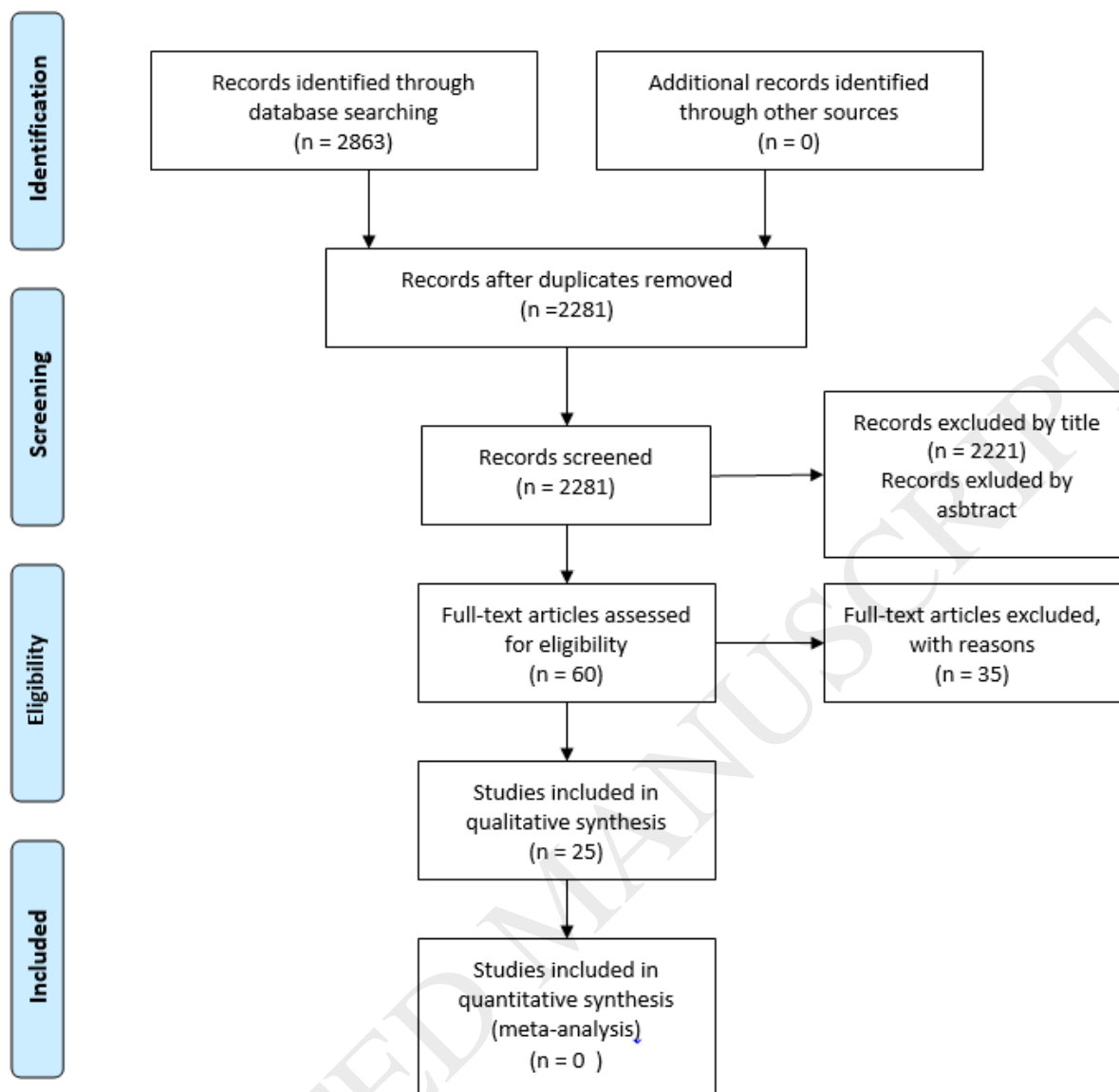
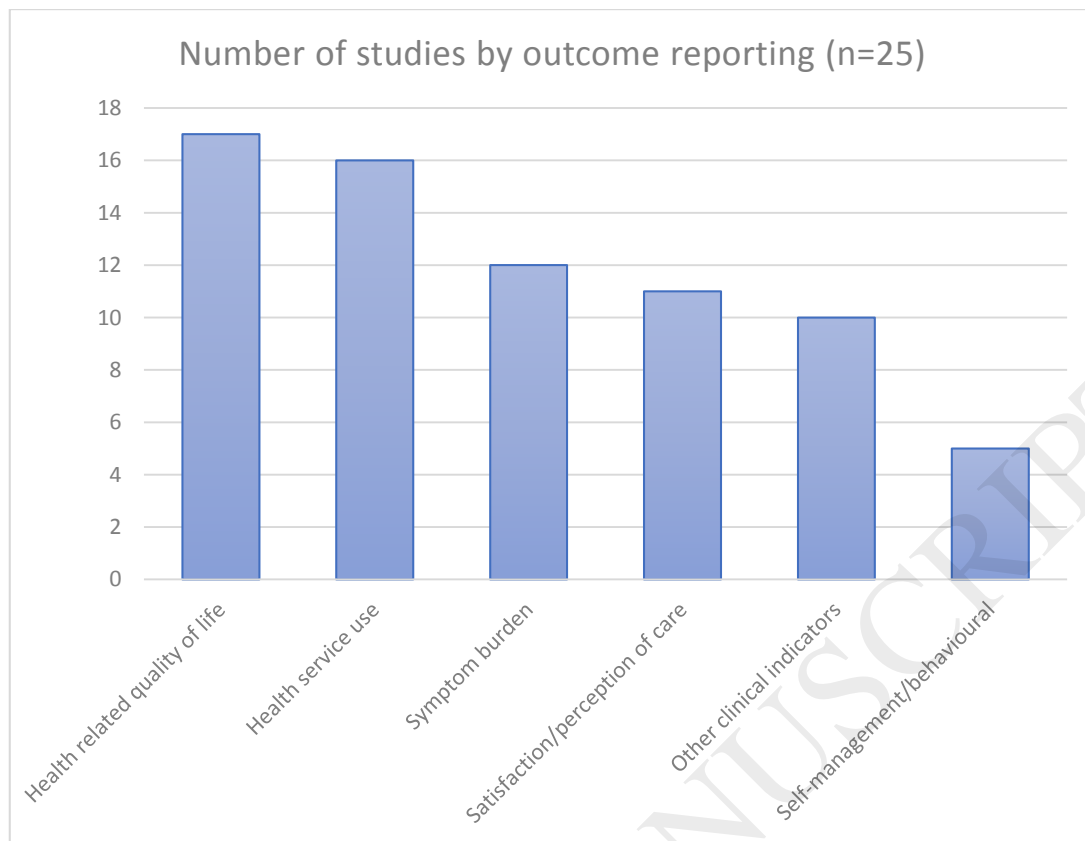**Figure 1. PRISMA Flow Chart**

Figure 2. Number of studies by types of outcome reporting (n=25)

Table 1. Characteristics and key findings of the included studies (n=25)

Author and Year Design, Sample Size, and Country	Setting and patient group	Intervention Arms	Outcome measures and follow up time points	Key findings	(1) Key components required to implement effective services (2) Was it clear that self-management support was a component of the intervention? (3) Was the nurse interventionist able to prescribe/adjust dosage of medications?
Martensson et al. 2005(19) Cluster RCT N=153 Sweden	Heart failure in primary care	Nurse-led intervention for patient self-management (1 extension education and counselling session lasting for 2 hours, with a 12-month telephone follow up period) Vs. Standard Care (team-based care including care from primary care physicians, nurse assistant nurses and a physiotherapist)	HRQoL using the SF-36 health survey and the Minnesota Living with Heart Failure questionnaire. Depression using the Zung Self-Rated Depression Scale Time of enrolment, baseline, 3 and 12 months	The intervention group reported significantly improved role function due to physical limitations (P= 0.008) and moderate/severe depression (p=0.023) at 3-month follow-up. No other significant between-group differences were reported.	(1) Training related to patient counselling that is targeted to specific diseases. The training was offered to primary care nurses and physicians by a heart failure nurse and a cardiologist. The program aimed at increasing the competence for providing heart failure care at the primary health care centres. (2) Yes (3) No
Nathan et al. 2006(21) RCT N=154 United Kingdom	Acute asthma outpatient discharge follow-up care	Nurse-led regular follow-up appointments (medical review, patient education, and a self-management asthma plan) vs. Doctor-led regular follow-up appointments Both arms received an initial 30-min follow up clinic appointment within 2 weeks after discharge and at 6 months	Number of exacerbations, Number of participants reporting exacerbations, Mean number of exacerbations per person, Hospital readmissions, Emergency nebulisation, HRQoL using the Asthma Questionnaire 20 and St. George Respiratory Questionnaire, change in peak flow, follow up clinics attended and arranged. 2-weeks and 6 months' post-discharge	Follow up by a nurse specialist for patients discharged from the hospital following acute asthma can be delivered equivocally compared to follow up delivered by a doctor. No significant difference in reported outcomes.	(1) Use of a structured intervention program delivered by an experienced specialist nurse. The intervention was pre-determined according to national and international guidelines. (2) Yes (3) Yes (nurse practitioner)
Ho et al. 2007(49)	Chronic heart failure	Nurse-led home and clinic based program incorporating telephone follow up (history taking, physical examination,	Economic evaluation of nurse-led program Pre-intervention and 6 months' post-intervention	Introduction of intervention was associated with an improved functional class (p<0.001), average fee for visiting emergency services	(1) Use of American College of Cardiology and American Heart Association guidelines for health failure management

Before and After study N=247 Taiwan		health education re. heart failure) vs. Standard care (pre-introduction of intervention)		(p=0.02). Frequency of visiting outpatient clinics increased (p<0.001).	(2) Yes (3) No
Huws et al. 2008(38) Before and After and controlled prospective trial Time point 1: 86,048 Time point 2: 86,294 United Kingdom	NHS Primary Care Practices Unplanned medical and geriatric hospital admission management	Nurse-led case management vs Standard care (pre-introduction of intervention)	Hospital admissions and re-admissions 12 months pre- and 12 months' post-implementation of intervention	In the intervention group, there were significantly improved rates of unplanned medical and geriatric admission lower (p=0.018), length of stay ≥1 night (p=0.015). There were no other significant differences reported	(1) An intensive (8-week) training was provided to the advanced practice nurses on individual patient management (2) No (3) No
Sorensen et al. 2008(26) RCT N= 102 Denmark	Chronic pain outpatient care	Nurse-led regular follow-up appointments (immediately after discharge from multidisciplinary pain centre, 4, 8, 12,16,20,24 months) vs Standard care (no additional follow up services)	HRQoL using the SF-36 health questionnaire, Cost intervention, Cost to healthcare services Baseline, 24 months	No significant difference in reported outcomes	(1) N/A (2) Yes (3) No
Willems et al. 2008(22) RCT N= 109 The Netherlands	Asthma follow-up care	Nurse-led tele-monitoring follow-up care vs Standard care	Asthma-related HRQoL using the AQLQ in adults and the paediatric AQLQ in children, clinical asthma symptoms, medical consumption, lung function Self-reported outcomes: Baseline, 4, 8, 12 months Lung function: baseline and 12 months	No significant difference in reported outcomes The tele-monitoring programon its own is no guarantee of success	(1) This followed an asthma management protocol based on the Global Initiative for Asthma guidelines and the Dutch College of General Practitioner. The nurse was able to decrease (after 3 months of stable asthma) or increase asthma medication by one step. (2) Yes (3) Yes

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Chan et al. 2009(24) RCT N=175 United Kingdom	Outpatient clinic for dyspepsia	Nurse Practitioner-led outpatient clinic vs Usual Care (General practitioner care)	Dyspepsia using the Glasgow Dyspepsia severity scores, Health status and HRQoL using the Health Status Short Form 12, weight, medication cost, use of ulcer healing drugs Baseline, 6 months	Intervention group reported a significant improvement in dyspepsia score (p<0.001), health status (p<0.001), medication costs (p<0.001), and consumed less full-dose proton pump inhibitors (p<0.001)	(1) Referral pathways to nurse-led clinics (2) Yes (3) Yes (Nurse Practitioners)
Dierick-van Daele et al. 2009(39) RCT N= 1501 The Netherlands	Community general practitioners clinics	Nurse Practitioner-led consultation for common complaints vs General practitioner-led consultation	Patient perceptions of quality of care, Effectiveness of the consultation and follow-up consultations, Medical resource consumption, Compliance with practice guidelines for general practitioners, Duration of consultation Baseline, Directly after the consultation, two weeks after the consultation.	Patients within the intervention group who reported at least one other disease were significantly more satisfied with their consultation (p value not reported),. Nurse practitioners spent an average of 12.22±5.7 in face-to-face contact with patients, compared with 9.20±4.8 minutes for GPs (P < 0.001). Patients within intervention group were most likely to be asked to return for additional consult than control (P=0.001) No significant difference in reported all other outcomes	(1) Use of experienced nurses to aid in rapport building, specialised education to prepare nurses for nurse-led roles (2) No (3) Yes (Nurse Practitioners)
Hill et al. 2009(27) RCT N=100 United Kingdom	Consultant rheumatology clinic (Osteoarthritis)	Nurse-led symptom management vs Junior physician care	Pain using a visual analogue scale, physical function assessed by duration of morning stiffness, self-efficacy using the arthritis self–efficacy scale, psychological health using the Arthritis Impact Measurement Scales, patient knowledge, satisfaction using the Leeds satisfaction Questionnaire Baseline, 16, 32, 48 weeks	No statistical significant differences) in outcomes between clinical nurse specialists and junior physicians in pain, morning stiffness, physical function and self-efficacy. Patients in the nurse-led group had significantly better knowledge and higher satisfaction of care (p value not reported).	(1) The clinical nurse specialists had open access to the rheumatologist for conferral or referral of patients (2) Yes (3) No
Verschuur et al. 2009(29)	Patients recently undergone intentionally	Nurse-led follow-up care vs standard care (surgeon-led care)	HRQoL using the EQ-5D, EQ-VAS, EORTC QLQ-OES18, and EORTC QLQ-C30 questionnaires,	Intervention group reported greater spousal satisfaction with care (P=0.03), Patients and spouses	(1) Use and training of specialised nurses, with experience over 10 years in cancer care

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				in control reported that the care received did fulfil their expectations and received more advice regarding disease management (P=0.04 and 0.03, respectively). Costs of intervention follow-up visits were significantly lower than those of standard follow-up visits (P<0.001). No significant difference in measures of QoL or other reported measures.	(2) No (3) No
RCT N=109 The Netherlands	curative surgery for oesophageal or gastric cardia cancer	Follow up for both groups: 6 weeks, 3, 6, 9 and 12 months	Patient and spouse satisfaction with care, medical costs HRQoL: baseline 4, 7, 13 months Patient satisfaction: 7 months Medical costs: 6 weeks, and 3, 6, 9, and 12 months		
Chow et al. 2010(31) RCT N=100 Hong Kong	Peritoneal dialysis unit and discharge for end-stage renal failure patients	Nurse-led discharge planning using motivational interviewing plus weekly follow-up meetings (6-weeks) vs Standard care (information, telephone hotline service, printed materials and a reminder to attend outpatient clinic)	HRQoL using the Kidney Disease Quality of Life Short Form Baseline, 6 weeks, 12 weeks	No statistically significant difference in QoL between groups. Statistically significant within-group effects were found for symptoms/problems, effects of kidney disease, sleep, role-physical, pain, emotional wellbeing and social function. Statistically significant interaction effects were demonstrated for staff encouragement, patient satisfaction, sleep and social function.	(1) The intervention protocol was developed by the researchers and reviewed by experienced renal nurses and physicians. Telephone interviews can be used effectively to improve clinical outcomes. (2) Yes (including patient and family members in the self-management intervention) (3) No
Blank et al. 2010(37) RCT N=238 United States of America	Community patients with HIV and serious mental health illness	Nurse-led in-home consultations and coordinated medical and mental health services (minimum one visit per week and coordinated clients medical and mental health care for 12 months) vs Standard care	Adherence to HAART, viral load and CD4 count Baseline, 3 months, 6 months, 12 months, 24 months	Greater level of HAART adherence in the intervention group compared to control at 6 and 12 months (p= 0.03 and 0.05, respectively). A subset and ITT analysis of the intervention group reported a significant difference in log10 viral load (p≤.001) at 12 months compared to baseline. No significant difference in CD4 count and detectable viral load was reported.	(1) The intervention was designed using a reasoned action model (2) Yes (3) No (the APN collaborated with prescribing providers, pharmacists and case managers to organise medication regimens)
Wong et al. 2010(50)	Renal outpatient care	Nurse-led follow-up care vs Standard care	Adherence to diet/fluid advice using a modified version of the dialysis diet and fluid	Patient satisfaction was higher in the intervention group at second	(1) Utilising staff and relevant stakeholders that hold rapport or

RCT N= 98 Hong Kong			non-adherence questionnaire, HRQoL using the Kidney Disease Quality of Life, patient satisfaction using the La Monica-Oberst Patient Satisfaction Scale, symptom and complication control, health service utilization Baseline, 7 weeks, 13 weeks	time point (p = 0.01). Significant differences for HRQoL measures relating to sleep and symptom (p<0.001). No other significant between-group differences reported.	skill-set relevant to the target population (2) Yes (3) No
Allen et al. 2011(20) RCT N=525 United States of America	Community health centres	Nurse practitioner-led intensive management program for patients with CVD risk factors (patients were followed for 12 year) vs Usual care combined with feedback on CVD risk factors	Lipids (TC, LDL-C, triglycerides), BP, HBA1C, patients' perceptions of the quality of their chronic illness care using the Patient Assessment of Chronic Illness Care Survey, lifestyle behaviours of dietary intake measured by the Habits and History Food Frequency Questionnaire, physical activity using the Stanford 7-day physical activity recall, HRQoL using the EQ5D Baseline, One year	Compared with control patients in the intervention group had significantly greater improvement in total cholesterol (p<0.001), LDL-C (p<0.001), triglycerides (p=0.013), systolic blood pressure (p=0.003), diastolic blood pressure (p=0.013), HbA1c (p=0.034), and perceptions of the quality of their chronic illness care (p=0.034)	(1) Strong collaboration between the NP and community health workers with an expertise of working with underserved minority populations is required. The NP and the Community Health Worker were trained in motivational interviewing behaviour change techniques. Treatment algorithms were pre-developed. (2) Yes (3) Yes (Provided by Nurse Practitioner)
Borbasi et al. 2011(23) Before and after, non-randomised, controlled, study N=320 Australia	Aged care facilities	Nurse Practitioner-led Dementia Outreach Service vs Standard care (without the Nurse Practitioner service)	HRQoL of patients as determined by staff using an amended version of the Dementia Quality of Life tool Authors self-designed questionnaires for assessing stress, knowledge, self-confidence of staff (no details on the validity of these questionnaires available) Baseline (pre-intervention), immediately after implementation of intervention, and 3-6 months' post-baseline	No significant differences were reported for all outcomes assessed, except for the increased level of staff self-confidence on the intervention group in comparison with the control group.	(1) The service was led by a NP, supported by a team including clinical nurse, endorsed enrolled nurse, assistant in nursing, clinical facilitator, social worker and administrative assistant. (2) No (3) Yes (provided by Nurse Practitioner)
Foreman et al. 2011(34) Non-Randomised, controlled intervention trial	ADHD clinic	Specialist Nurse-led follow-up consultation vs Physician-led consultation	Clinical symptoms using the Strengths and Difficulties Questionnaire, side-effects using a clinic-developed side-effect questionnaire, patient satisfaction using the Commission for Health Improvement patient satisfaction questionnaire Follow up time points not available	No significant differences reported	(1) The service needs to be provided by a Specialist Nurse with prescribing right – non-medical prescribing qualification) (2) No (3) Yes (as above)

N= 70 United Kingdom					
Houweling et al. 2011(35) RCT N=230 The Netherlands	Diabetes management	Nurse-led diabetes management vs Standard care (GP Care)	HbA1c, Blood pressure, cholesterol measures, glycaemic control, changes in treatment (referrals, drug intensification), HRQOL using the SF-36, patient satisfaction, healthcare consumption Baseline, 14 months	In the intervention group, there was a greater level of referrals to an ophthalmologist (p=0.07), referrals to insulin therapy (p=0.015), measures to prevent diabetic foot symptoms (p=0.001), and mean number of visits (p<0.001). There were no other significant differences reported.	(1) The two Practice Nurses received one week training on a detailed treatment and management protocol. These nurses were also empowered to prescribe/adjust medications and order laboratory tests. (2) No (3) Yes (the PNs were non nurse practitioners who were allowed to prescribe 14 different medications and to adjust dosages for a further 30)
Kneipp et al. 2011(40) RCT N=432 United States of America	Community chronic disease management	Nurse-led 9-month intervention vs waitlist group	Depression using the BDI-II tool, General health and HRQoL using the SF-12v2 questionnaire, functional status using items from the SF-12v2, Health care knowledge and use Baseline, 3 months, 6 months, and 9 months	Intervention group reported statistically significant improvement in depression and functional status scores (p=0.016 for each), healthcare use (p=0.007) and Medicaid knowledge (p<0.001)	(1) The skill building in women was grounded within the Transactional Model of Stress and Coping, and employed cognitive behavioural stress management therapy techniques. The intervention was specifically helping participants to be gain a range of relevant self-management and coping skills. (2) Yes (3) No
Iglesias et al. 2013(41) RCT N= 1461 Spain	Community management of low complexity diseases	Nurse-led consultation vs Consultation with General Practitioner	Patient satisfaction; resolution of symptoms; rates of revisit for same symptoms, hospital admissions, duration of the visit, patient perceived quality of care, use of resources on drug prescriptions and sick leave, the patient's preference of care Two weeks' post-consultation	No significant difference between intervention and control group reported	(1) Nurses were trained in relation to treatment guidelines for common diseases; and was provided with referral pathways for more complex cases. Nurses could also access to an electronic application which included the guideline, designed as a decision-making support tool. (2) No

					(3) Yes (Nurses were not nurse practitioners, but were empowered to prescribe)
Larsson et al. 2014(28) RCT N= 107 Sweden	Rheumatology clinic	Nurse-led 6-month consultation vs Rheumatologist-led consultation	Disease severity using the DAS28 and DAS-CRP, patient satisfaction with care, CRP, HRQoL using the HAQ, pain using VAS Baseline, 6 months, 12 months	Statistically significant (but non-clinically) difference in CRP (p=0.03) between intervention and control at 12 months. There was no other significant difference in outcomes.	(1) Nurses had extensive experience (with 22-39 years of experience and 9-20 years of experience of managing rheumatic diseases). Nurses had access to rheumatologists as required. They received special training from a rheumatologist and RA instructor (2) Yes (3) No
Murfet et al. 2013(36) Uncontrolled pre-post intervention audit N=261 Australia	Gestational diabetes care	Nurse Practitioner-led diabetes management program vs Standard care	HBA1C, Healthcare referrals and use, adverse maternal and neonatal events Pre-intervention: July 2003–June 2006, Post-intervention: January 2010–December 2011	During the post-intervention period, there was a statistically significant increase in referrals to dietitians and diabetes educators and insulin use, a significant decrease in referral to physicians for diabetes care and adverse neonatal outcomes (p<0.0001 for all measures).No significant difference in HbA1c and maternal adverse outcomes.	(1) The nurse-led model is supported by dietitians and diabetes educator at the same location of the nurse-led clinic. Nurse-led care is guided by an evidence-based screening and management protocol (2) No (3) Yes (Delivered by Nurse Practitioner)
Young et al. 2013(30) RCT N=755 Australia	Post-surgery for colorectal cancer	Nurse-led telephone follow-up care at 3, 10 days, 1,3,6 months vs Standard care	HRQoL using FACT-C, Distress Thermometer tool, Supportive Care Needs Survey Short Form (SCNS-SF 34), Postoperative health services utilization (unplanned readmissions; emergency room presentations), patient experience of cancer-care coordination Baseline, 1, 3, and 6 months after discharge	No significant difference in reported outcomes	(1) A tailored approach might be required, as this intervention did not have any benefits according to the results. (2) No (3) No
Walker et al. 2014(32) Before and After Study	Community renal patients	Nurse Practitioner-led education and individualised care	Change in proteinuria, eGFR, 5-year absolute CVD risk, blood pressure, serum total cholesterol, HbA1c, BMI, overall self-management, overall medical knowledge adherence to medication and adoption of a healthy lifestyle	Significant improvements in proteinuria (p=0.002), eGFR (p=0.002), 5-year absolute risk reduction (p=0.002), systolic and diastolic blood pressure (p<0.01 and p<0.001, respectively),	(1) Use of a nephrology nurse (Additional qualifications, able to work autonomously, and assess, diagnose and prescribe within their scope of practice) (2) Yes

				cholesterol (p=0.002), HbA1c (p<0.001), active smoking (p=0.003), overall self-management score (p<0.001), medication knowledge (p<0.001), knowledge of condition (p<0.001), healthy lifestyle (p<0.001), number of prescribed hypertensives (p<0.001), HMG-COA reductase inhibitors (p=0.003), and aspirin (p<0.001)	(3) Yes
N=52 Australia			Baseline, 3, 6, 9 and 12 months		
Hernandez et al. 2014(25) RCT N=286 United Kingdom	Post-Intensive care	Nurse-led intensive care follow-up clinics vs Standard care (no intensive care follow up after hospital discharge, follow up by their GP as required)	HRQoL using the SF36, EQ-5D, depressive symptoms, anxiety (Hospital Anxiety and Depression Score) and post-traumatic stress (David trauma score), use of other primary and secondary care resource use, Resource use and cost of the nurse-led clinics, Use and cost of medications Baseline, 6 months, 12 months	There was no difference in EQ5D, SF36, depressive symptoms, anxiety and post-traumatic stress at 6 months or 12 months. Nurse-led intervention was more expensive than standard care (£5,789 for standard care and £7,577 for intervention). No significant difference in any other reported outcome.	(1) The format and content of the intervention was guided by national guidelines, national survey of practices, and the extensive experience of the clinicians. A Consultant Intensivist was available as required. (2) No (3) No
Buszewicz. 2016(33) RCT N=558 United Kingdom	Community mental health (chronic depression)	Nurse-led regular follow-up appointments Vs Standard care (GP-led care)	Depression severity using the BDI-II, HRQoL using the EQ-5D, DSM-IV diagnosis and frequency of depressive episodes assessed using the CIDI questionnaire, functional impairment using the Work and Social Activity Scale; Practice Service Data on GP visits, practice nurse contacts, referrals for psychological therapy and prescription for psychotropic medication Baseline, and 24 months. Depression: baseline, 3, 6, 12, 18, and 24 months	No significant difference in depression scores between groups. Functional impairment significantly improved in the intervention group compared to the control group (P=0.010). Intervention group had a higher number of nurse visits and months on anti-depressant medications compared to control (P=0.026 and 0.047, respectively). No statistically significant difference in diagnostic category reported (P=0.368). Contamination-adjusted ITT analysis found significant improvement in depression	(1) Adequate training specific to the disease population concerning mental illness, use of motivational interviewing to improve intervention adherence (2) Yes (3) No (number of prescription of psychotropic medication was assessed between the two groups. However, it was not explicit whether the nurse was able to prescribe).

				(P=0.004) and QoL (P=0.004) scores per nurse treatment-session	

Note.

AQLQ, Asthma Quality of Life Questionnaire; BDI-II, Beck Depression Inventory-II; BMI, Body Mass Index; CRP, C-reactive protein; CVD, cardiovascular disease; DAS28, Disease Activity Score; DSM, Diagnostic and Statistical Manual of Mental Disorders; eGFR, Estimated Glomerular Filtration Rate; EQ5D, EuroQol 5 Dimension; EQ-VAS, EuroQol Visual Analogue Scale; EORTC QLQ European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-C, Functional Assessment of Cancer Therapy-Colorectal; HAART, Highly active antiretroviral therapy; HAQ, Health Assessment Questionnaire; HMG-COA, Hydroxymethylglutaryl-CoA; ITT, Intention To Treat; HRQoL, Health Related Quality of Life; NHS, National Health Service; SF-36, Short Form Health Survey-36

Table 2. Risk of Bias Assessment of the included studies (n=25)

Study ID	Random sequence generation	Allocation Concealment	Blinding of participants	Blinding of outcome	Incomplete data	Selective Outcome Reporting	Other sources of bias
Martensson et al. 2005	L	H	H	H	L	U	L
Nathan et al. 2006	L	U	H	L	L	H	L
Ho et al. 2007	N/A	N/A	H	H	U	U	H
Huws et al. 2008	N/A	N/A	H	H	U	L	H
Sorensen et al. 2008	L	L	H	H	H	H	L
Willems et al. 2008	L	H	H	H	H	L	H
Chan et al. 2009	L	L	H	L	L	H	L
Dierick-van Daele et al. 2009	L	L	H	H	L	L	L
Hill et al. 2009	L	L	H	L	L	U	L
Verschuur et al. 2009	L	L	H	H	L	U	L
Chow et al. 2010	L	U	H	U	L	L	L
Blank et al. 2010	L	L	H	L	L	L	L
Wong et al. 2010	L	L	H	L	H	U	L
Allen et al. 2011	L	U	H	H	L	H	L
Borbasi et al. 2011	N/A	N/A	H	H	H	U	H
Foreman et al. 2011	H	H	H	H	H	U	H
Houweling et al. 2011	L	U	H	U	L	L	U
Kneipp et al. 2011	L	L	H	H	L	U	L

Iglesias et al. 2013	L	L	H	L	L	L	U
Larsson et al. 2013	L	L	H	H	H	U	L
Murfet et al. 2013	N/A	N/A	H	H	L	U	U
Young et al.2013	L	L	H	H	L	L	L
Walker et al. 2014	N/A	N/A	H	H	L	L	L
Hernandez et al. 2014/ Cuthbertson 2009	L	L	H	H	L	L	L
Buszewicz. 2016	L	L	H	L	L	L	L

*Other sources of bias include: recruitment (selection bias), measures of exposure, measure of outcome, confounding factors and high lost to follow up. L=Low, U=Unclear, H=High, N/A= Not applicable as not RCT

Table 3. Characteristics and results of the cost utility and consequences studies (n=5)

	Hernandez 2014	Sorenson 2008	Verschuur 2009	Ho 2007	Chan 2009
Country	UK	Denmark	The Netherlands	Taiwan	UK
Trial design	Pragmatic, non-blinded, multicentre RCT, n=286	Prospective, RCT, n=102	Prospective RCT, n=109	Pre- post design, 6 months ea, n=247	RCT, n=175
Patient group	Critical care patient	Pain	Oesophageal cancer	Chronic heart failure	Dyspeptic patients after gastroscopy
Economic design	Cost-utility	Cost consequences	Cost-utility	Cost consequences	Cost consequences
Time horizon	12 months post-intervention	2 years (costs pre-post)	12 months post	6 months pre and post	6 months
Intervention	Intensive care unit follow-up, base, 3, 9 months, self-directed	Home visits every 4 months (7x)	Home visits + In-hospital visits,6 weeks, 3,6,9,12 months	Home visits every 2 weeks initially, then OPD 2-3 mthly, & telephone 3-4 weekly	Nurse outpatient
Comparison	Standard care (GP & specialist)	Standard care (GP allowed)	Standard care (In- hospital visits,6 weeks, 3,6,9,12 months)	intervention group are their own comparisons - pre intervention.	Usual care - GP follow-up
Perspective	UK NHS perspective	Health service	Not stated	Not stated	Pharmacy costs only
Main outcomes	Costs, QALYs using EQ5D at baseline, 6, 12 months	Costs (GPs, hospital, intervention), SF-36 at 4 times,	Costs (hospital, dx, treatments), EQ5D	Costs (outpatient, emergency dept, ward)	Drug costs, SF12, QoL, satisfaction
Main results	intervention £7,577, 0.60 QALYs SC £5,789, 0.58 QALYs	No diff in SF36 at all, right direction though, intervention incr GPs and lowered hospitals, €4004 intervention group, €7464 in control group (ns)	EQ5D improved in both groups (ns), €2592 vs €3789 in intervention favour (ns). Less inpatient admissions.	Pre US$624,020, post US$362,722 (42% less) Readmissions – same ALOS – lower 20 vs 14 days, ED lower 37%. Improved compliance and knowledge of meds	Qol stat sign better in intervention Lower ulcer healing drug use in intervention and cost savings £39.6 over 6 months
Conclusion by authors	Not cost effective with SC =93% probability at <£20,000 per QALY	No patient effects, big cost savings in intervention group (ns)	Cost saving 91% prob, WTP €0, ignoring QoL effects	Decreased hospital and LOS and cost-savings	Good all round. Full CEA needs to be done.