NURSE PRACTITIONER IMPACT ON QUANTITATIVE PATIENT OUTCOMES IN FOUR HEALTHCARE SETTINGS' SYSTEM CONTEXT:

A SYSTEMATIC REVIEW

AND

META-ANALYSIS

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ABSTRACT

Nurse Practitioners (NPs) are frequently integrated into interprofessional teams to improve quality and efficiency of healthcare delivery, especially in complex systems. Research on the NP role has grown dramatically, yet an aggregate analysis had never been performed. The purpose of this review was to systematically describe the nature and impact of NP interventions in healthcare settings, to establish a comprehensive understanding of NPs with respect to healthcare delivery, including discovery of information gaps. The specific objectives of the study were to describe the types of: 1) intervention activities that NPs have performed in randomised controlled trials (RCTs); 2) quantitative study endpoints measured in RCTs; and 3) impact of NPs on all quantitative patient outcomes in four settings: primary health care, long term care, outpatient care, and acute care, conducting meta-analysis where possible. Eligible studies included low risk of bias RCTs that tested NP interventions on quantitative endpoints in healthcare settings; data sources included peer reviewed or grey literature in English, from the year 2000 forth. The literature search performed by a professional librarian (MH) yielded 1,188 unique citations. Screening for relevance and risk of bias by two independent reviewers (LT and NL) resulted in a set of included studies comprised of 39 articles (29 different RCTs). Data extraction by LT was cross-checked by the second independent reviewer NL. Findings were systematically summarized according to pre-specified protocol. Out of 89 classes of endpoint-outcomes, results for 43 patient outcome classes (43/89; 48%) were statistically significant, associated with 26/29 (90%) interventions. Meta-analysis was conducted to compare the proportion of hospitalizations between intervention and control groups of two homogenous studies, systematically completing the review's data analysis. Transparent data presentation within an explicit, reproducible methodology minimizes bias, resulting in reliable findings that were organized, synthesized and summarized in a clear and comprehensive fashion. To the extent of its findings, this systematic review may support improvements in access to quality healthcare, and may provide insight into long term strategies that have potential to contribute toward enhanced balance within the healthcare continuum, from delivery of preventive primary health care services to treatment in acute care.

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DEDICATION

This thesis is dedicated to my amazing children
Robert Paul Tremblay, Nicole Jacqueline Tremblay, Stephen John Tremblay, and
Christopher Philip Tremblay, to my courageous mother
Mrs. Mary C. Goldak, and to my late father
Dr. George R. Goldak, whose inspiration continues unending.

With true, heartfelt sincerity, this thesis is also dedicated to all those within our health systems who are *most* vulnerable, and in *greatest* need of services and care.

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LIST OF ABBREVIATIONS

NP	Nurse Practitioner
CNS	Clinical Nurse Specialist
APN	Advanced Practice Nurse
PHC	Primary Health Care
PHCNP	Primary Health Care NP
PSYNP	Psychiatric NP
ACNP	Acute Care NP
ANP	Advanced NP
ARNP	Advanced Registered NP
NNP	Neonatal NP
RCT	Randomised Controlled Trial
IPT	Interprofessional Team
RS	Role Substitution
CNA	Canadian Nurses Association
CMA	Canadian Medical Association
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
PROSPERO	International Prospective Register of Systematic Reviews
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
BMI	Body Mass Index
DBP	Diastolic Blood Pressure
SBP	Systolic Blood Pressure
CABG	Coronary Artery Bypass Graft
CHD	Coronary Heart Disease
CHF	Chronic Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
ED	Emergency Department
ER	Emergency Room

ESP	Extended Scope Physiotherapist
GP	General Practitioner
JHD	Junior House Doctor
ICU	Intensive Care Unit
SHO	Senior House Officer
LDL-C	Low Density Lipoprotein Cholesterol
HDL-C	High Density Lipoprotein Cholesterol
MCID	Minimal Clinically Important Difference
MET	Metabolic Equivalent
NSAID	Non-Steroidal Anti-Inflammatory Drug
CI	Confidence Interval
ICC	Intraclass Correlation Coefficient
OR	Odds Ratio
RR	Risk Ratio
SD	Standard Deviation
CE	Cost-Effectiveness
CEA	Cost-Effectiveness Analysis
QOL	Quality of Life

Please note: regarding the term A1c Hemoglobin, 'A1c' is not an acronym but refers to the order of elution of chromatographic hemoglobin fractions.[1]

GLOSSARY

Nurse Practitioner (NP) - Registered Nurse (RN) with additional educational preparation and experience who possesses and demonstrates the competencies to autonomously diagnose, order and interpret diagnostic tests, prescribe pharmaceuticals and perform specific procedures within their legislated scope of practice.[2]

Primary Health Care (PHC) - a basic level of health care that includes programs directed at the promotion of health, prevention of disease, and early diagnosis of disease or disability, provided in an ambulatory facility to people often living in a particular geographic area; [3] essential health care made universally accessible to individuals and families through their full participation, at a cost their community and country can afford; includes broad determinants of health (e.g. food security, environment, housing, education, socioeconomic status, social support networks, integrated health services) and the principle of appropriate technology: modes of care that are appropriately adapted to the community's social, economic and cultural development, as alternatives to high technology, high cost services, through innovative models of health care that disseminate research results.[4]

Primary Care - first contact care that leads to a course of action to resolve the health problem; illness oriented, and may include preventive, curative, and rehabilitative care; focuses on health care services often provided by a physician, may be provided by a nurse, and may include emergency room visits; a narrow component of the broader concept of primary health care.[3,4]

Long Term Care - provision of medical, social, and personal care services on a recurring or continuing basis to persons with chronic physical or mental disorders, in environments ranging from institutions to private homes, for patients of all age groups.[3]

Outpatient / Specialized Referral Care - treatment of a patient not admitted overnight to hospital, in an office, clinic or other ambulatory care facility.[3]

Emergency Department (ED) / Acute Inpatient Care - treatment in a hospital, where inpatient care requires admission to a hospital or other healthcare facility for at least an overnight stay.[3]

Interprofessional Team (IPT) mode of NP implementation - the NP practices with at least one other health care provider to deliver patient / client care.

Role Substitution (RS) mode of NP implementation - the NP acts as a replacement for another health care provider, and is delegated the responsibilities of diagnosing, prescribing, and overseeing patient care; relates to the formal origin of the NP role in Canada in 1973 to create alternative health care services where / when physician shortages were being experienced.[5]

IPT Study - mutually exclusive to a role substitution (RS) study.

Program Study – tests an intervention program delivered by the NP(s) or a team of health professionals that may include a NP.

E.g. Web-based program study (IPT study) tests the effectiveness of a web-based platform on the management of diabetes, rather than NP care provision per se.[6,7]

E.g. PALSA (Practical Approach to Lung health in South Africa) program study (IPT study) tests the effectiveness of educational outreach in the case management of priority respiratory diseases, delivered by NPs.[8]

Diagnosis - the identification of a disease or condition by a scientific evaluation of physical signs, symptoms, history, lab test results and procedures.[3]

Open diagnosis - detection and management of any type of condition, disease, or risk factor for disease.

Limited diagnosis - detection and management of various types of conditions, diseases, or risk factors for disease, based on assessment of data limited by inclusion criteria and / or protocol.

Diagnosis of disease status - restricted to the detection or risk stratification of specific conditions / status of disease, often guided by protocols or algorithms forming the basis of the intervention.

Wellness Diagnosis - focuses on strengths that reflect an individual's transition to higher levels of wellness, where 'wellness' is a dynamic process of progress toward maximizing an individual's potential. Wellness diagnoses detect progression from one level of wellness to a higher level of wellness, by facilitating healthy responses for attainment of higher levels of health oriented goals.[9]

E.g. of wellness diagnosis = 'Health-seeking behaviour regarding weight-loss diet'

Health-seeking behaviors - active seeking of ways to alter personal health habits and/or the environment, by a person in 'stable health', in order to move toward a higher level of health.[10]

Stable health - achievement of age-appropriate illness-prevention measures; client reports good or excellent health, and signs and symptoms of disease, if present, are controlled.[10]

Prescribing Pharmaceuticals - to write an order for a drug or treatment.[3]

Open prescribing - conducted for the purpose of managing any type of condition, disease, or risk factor for disease.

Limited prescribing - conducted for the purpose of managing various types of specific conditions, diseases, or risk factors for disease based on data limited by inclusion criteria and / or protocol.

Procedures - the sequence of steps to be followed in establishing some course of action.[3]

Education - intellectual, moral and social instruction, giving information on a particular subject.[11]

Strategies for Behaviour Change - an interactive helping process focusing on the needs, problems, or feelings of the patient and significant others, to enhance or support coping,

problem-solving, behaviour change and interpersonal relationships, including relationships with the health care team.[3] E.g. 'Motivational interviewing' increases patients' awareness of 'readiness to change,' to subsequently create attainable goals toward a healthier lifestyle.[12]

Care Coordination - activities delivered from a remote site via telephone or email, often requiring patient referrals to appropriate services based on a limited assessment; not completely classified within the traditional categories of diagnosis, prescribing, clinical procedures, or strategies for behaviour change / education.

Preventive Healthcare - to hinder the occurrence of an illness or to decrease the incidence of a disease;[3] reducing risks or threats to health.[13]

> **Primary (1^0) Prevention** - aims to prevent disease or injury before it ever occurs, by preventing exposures to hazards that cause disease or injury, altering unhealthy or unsafe behaviours that can lead to disease or injury, and increasing resistance to disease or injury should exposure occur.[13]
>
> **Secondary (2^0) Prevention** - aims to reduce the impact of a disease or injury that has already occurred, by detecting and treating disease or injury as soon as possible, to halt or slow its progress.[13]
>
> **Tertiary (3^0) Prevention** - aims to soften the impact of an ongoing illness or injury that has lasting effects, by helping people manage long-term, often complex health problems and injuries (e.g. chronic diseases, permanent impairments).[13]

CONSORT (Consolidated Standards of Reporting Trials) provide guidance to facilitate clarity, completeness, and transparency of reporting of all randomised controlled trials. Explicit descriptions, not ambiguity or omission, best serve the interests of all readers, and model the development of guidelines for reporting systematic reviews and meta-analyses of studies evaluating interventions, the explicit goal being, to improve reporting.[14]

Systematic Review attempts to identify, evaluate and summarize all available evidence addressing a specific research question(s), with key characteristics including: clearly stated set of objectives with pre-defined eligibility criteria for studies; an explicit, reproducible methodology to minimize bias, thus providing more reliable findings; a systematic search that attempts to identify all studies meeting eligibility criteria; an assessment of risk of bias of the included studies; and a transparent, systematic presentation and synthesis of the characteristics and findings of the included studies, according to pre-specified protocol.[15]

Meta-Analysis is the use of statistical methods to summarize the results of independent studies; many systematic reviews contain meta-analyses. By combining information from all relevant studies (two or more primary studies that addressed the same hypothesis in the same way) from a review whose methods were valid and reliable (reproducible), meta-analyses can provide more precise estimates of the effects of health care interventions than those derived from the individual studies included within a review. Meta-analyses also facilitate investigations of the consistency of evidence across studies, and the exploration of differences across studies.[15]

1. Introduction

Delivery of healthcare services in a world with limited resources and increasing pressure to create evidence-based quality patient outcomes[16] may require interprofessional teams. Interprofessional teams (IPTs) are defined by Virani as various healthcare disciplines working together toward common goals to meet the needs of a patient population.[17] One strategy to improve the efficiency and effectiveness of IPTs is to employ the services of an advanced practice Nurse Practitioner (NP). In Canada, NPs are defined as "registered nurses with additional educational preparation and experience who possess and demonstrate the competencies to autonomously diagnose, order and interpret diagnostic tests, prescribe pharmaceuticals and perform specific procedures within their legislated scope of practice."[2] The demand for NPs in Canada continues to grow due to increasing recognition of their roles as clinical experts, leaders and change agents for improving access to high-quality, cost-effective and sustainable healthcare.[18]

1.1 Statement of Problem

The body of research on the NP role has grown dramatically over past years. As a result, independent studies examining the effect of NPs are widely available but an aggregate analysis of these healthcare providers had never been performed. The systematic assessment of quality, consistency, effectiveness, and scope of this review allows for a comprehensive understanding of the current state of knowledge (including information gaps) about NPs with respect to healthcare delivery.

1.2 Purpose of Study

The purpose of the study was to systematically describe the literature pertaining to the nature and impact of nurse practitioner interventions in healthcare settings. The specific objectives of the study included 1) describing the types of activities that NPs have performed in randomised trials; 2) describing the types of endpoints evaluated; and 3) describing the impact of NPs on all quantitative patient outcomes, conducting a meta-analysis to measure the impact of NPs on patient outcomes from homogeneous studies where possible.

1.3 Significance

NPs in Canada are frequently being incorporated into IPTs to improve the quality and efficiency of healthcare delivery, especially in complex systems.[19] In order to invest in NPs most effectively, a clear understanding of their roles and impact on patient outcomes is needed, especially with respect to IPTs, recognized as potentially, the most cost-effective model of quality care delivery.[20]

2. Literature Review

2.1 History of the Nurse Practitioner Role

In Canada, NPs are defined as "registered nurses with additional educational preparation and experience who possess and demonstrate the competencies to autonomously diagnose, order, and interpret diagnostic tests, prescribe pharmaceuticals and perform specific procedures within their legislated scope of practice."[2] NPs were introduced in remote regions and southern urban settings throughout Canada in an attempt to alleviate the shortage of family physicians in the early 1970s.[21] By the late 1970s, it was suggested that NPs in Canada could help achieve the essence of primary health care according to its five principles of accessibility, public participation, health promotion, appropriate technology, and intersectoral cooperation.[4,22] However, for various reasons including a lack of NP role legislation, by the mid-1980s, NPs "disappeared in all but remote areas and a few sites in southern Canada."[23] Ten years later, provincial and federal governments called for major primary health care reform, and so the role of the NP was again considered a viable strategy to deliver health care services.[23] A $25 million Nursing Research Fund was created by Health Canada[24] which supported several projects around the NP role including a landmark report in 2010 by DiCenso and Bryant-Lukosius on advanced practice nursing entitled "Clinical Nurse Specialists and Nurse Practitioners in Canada: A Decision Support Synthesis."[18] However, despite the increased research activities devoted to the NP's role in Canadian health care settings, an aggregate evaluation of their activities and /or impact on patient care had never been undertaken.

DiCenso & Bryant-Lukosius made 11 recommendations for the following professional groups: the Nursing Community and its Partners, Senior Decision Makers in Policy and Practice, Educators, and Researchers, in order to guide positive change in both nursing role development and implementation.[25] However, despite the very comprehensive approach taken to the creation of this report, these 11 recommendations were based on summaries of various types of evidence ranging from randomised controlled trials (RCTs) to focus groups and interviews,[18] along with theoretical benefits of the NP role. Notably, a systematic review was not undertaken.

2.2 Role of the Nurse Practitioner

The NP role was developed to ensure timely access to high-quality, cost-effective care for positive patient outcomes.[5] At present, potential advantages of the NP role include increased access to care in primary healthcare services, especially for vulnerable groups, such as those in rural remote regions or Aboriginal people. As well, NPs may facilitate

improvements in chronic disease management, nursing home care, emergency department wait times, or in special populations such as neonatology, cardiology, neurosurgery, or intensive care.[26] It has also been suggested that the incorporation of NPs can result in lower health care costs.[27] However, it is not currently clear whether the potential to reduce health care costs is associated with NP roles specifically or with nursing interventions in general.[28] Although many individual studies of NP interventions can be identified, the nature and consistency of the evidence examining exclusively NP interventions has never systematically been summarized.

2.3 NP Implementation: Role Substitution or Interprofessional Teams

Over the years, NPs have assumed various health care functions depending on the setting and the needs of the community. Originally, NPs were primarily involved in role substitution activities to allow alternative health care services to be provided when physician shortages were being experienced.[29]Although role substitution has its informal origins in outpost nursing of the 1890s, in areas such as the Northwest Territories, Labrador and Newfoundland,[21] its formal origins in Canada occurred in the early 1970s. Parameters of the formal NP role were initially based on the educational program developed in1971 by the Faculty of Medicine and the School of Nursing at McMaster University, supported by the Ontario Ministry of Health[30] in response to physician shortages in southern urban Ontario.[5] The joint statement issued in 1973 by the Canadian Medical Association and the Canadian Nursing Association, further outlined these parameters.[5] Research on the NP role originally focussed on role substitution (RS), whereby NPs act as a replacement for the physician and are delegated the responsibilities of diagnosing, prescribing, and overseeing patient care. More recently, studies have focused on the benefits of adding NPs to interprofessional teams. For the purpose of this systematic review, an interprofessional team (IPT) is defined as the presence of at least one other health care provider working with the NP to deliver patient care, with an IPT study mutually exclusive to a RS study. As discussed above, team-based health care is considered a possible strategy to improve both efficiency and quality of health care in Canada.[17,19] However, the most beneficial activities undertaken by NPs in the context of IPTs are not known.

2.3.1 NPs in Role Substitution.

Several studies suggest that appropriately trained nurses can produce high quality care and patient outcomes equivalent to primary care doctors. Laurant and colleagues performed a systematic review of role substitution studies (RCTs; controlled before and after; and interrupted time series) with various nursing professionals (NPs, Clinical Nurse Specialists,

or other practice nurses) working as an intervention-substitute for usual care provided by a primary care physician (could include GPs, family doctors, pediatricians, general internists or geriatricians). This systematic review found nurses tended to provide more health advice and achieve higher levels of patient satisfaction compared to doctors.[28] Another systematic review was published on the impact of nurses in only primary / community care, in this case, via RS and IPT, but NP studies were excluded.[31] Horrocks and colleagues conducted a systematic review specifically regarding NPs as a first point of contact in primary care via RS, and concluded that increased availability of NPs would likely lead to high quality care with high levels of patient satisfaction.[32] Specifically within the acute environment, another systematic review evaluated the use of NPs in RS or IPTs, to reduce overcrowding in both urban and rural emergency departments, suggesting that NPs may represent a viable, effective patient-management option.[33] Clearly, systematic reviews have been performed on NP-related research but none have been performed to provide an aggregate analysis of the NP role exclusively in and of itself, in both upstream primary care / community environments as well as in downstream outpatient / inpatient hospital environments.

2.3.2 NPs in Interprofessional Teams.

Several studies suggest NPs can facilitate important benefits to patient outcomes when participating in interprofessional teams (IPTs). Integration of NPs and pharmacists into a primary care network for the provision of chronic disease management services resulted in improved quality of care indicators.[34] However, the extent to which these findings translated into improved patient outcomes was not examined. Significant improvements in patient outcomes and patient satisfaction were demonstrated through a NP-physician team approach to chronic disease management in a teaching hospital at modest incremental costs.[35] However, in a large academic medical centre, Ettner and colleagues found that inpatient care using NPs in multidisciplinary teams was associated with cost savings compared to usual care. In this study, patients' perceptions of care and quality of life were at least as good in the intervention as in the standard care group along with comparable patient health outcomes in both groups.[36]

Current knowledge about the benefits of NPs in health care settings is largely based on theoretical applications of the NP scope of practice along with various studies that examine diverse roles, settings, and endpoints. While it is possible that there are quite substantial benefits to be gained through use of NPs, the impact and roles of these health care practitioners have not been examined exclusively. A systematic review was undertaken to describe the current state of evidence and also to identify areas where evidence is lacking.

Establishing a clear and comprehensive understanding of the current state of knowledge about NPs with respect to healthcare delivery through the conduct of this systematic review will enable a more meaningful investment in their services, particularly for the potential enhancement of IPTs.

2.4 Purpose, Research Questions, and Hypotheses

The purpose of the study was to systematically describe the literature pertaining to the nature and impact of nurse practitioner interventions in health care settings. The specific research questions included:

1) What types of intervention activities have been performed by NPs in randomised trials?
2) What types of endpoint-outcomes have been quantitatively measured in randomised trials examining the impact of NPs?
3) What is the impact of the NP on patient outcomes in each of four practice environments: primary health care, long term care, outpatient care / specialized referral care, and emergency department / acute inpatient hospital care?

Patient outcome data associated with NP practice in and of itself, in all four practice environments had not been known in the context of a systematic review. Research question three addressed this unknown with its directional hypothesis of beneficial NP impact on patient outcomes in each of the four different practice environments examined in this review. Each practice environment represented the "common ground" / constant variable for potential sets of calculations comparing the effect of the NP intervention to standard practice without NP intervention. Patient outcome data derived from RS or IPT studies are both outcome data from implementation of the same NP role defined by the CNA, measuring the effect of the NP according to the logic of random assignment, attributing differences between treatment and control groups to the effect of the intervention.[37]

Two hypotheses were developed prior to undertaking this systematic review. First, it was expected that studies examining NPs in the context of role substitution (RS) would not find significant differences in patient outcomes compared to an active control. In these studies, control patients are typically managed by licenced health care providers such as physicians and specialists who likely provide a high level of care at baseline. In contrast, a second hypothesis was developed for studies examining the benefits of NP interventions in the context of interprofessional teams (IPTs). NPs providing care in this context were expected to demonstrate significant improvements in patient outcomes compared to usual care. Accordingly, determination of a combined effect from pooling RS and IPT studies was

not expected to be undertaken due to the predicted differences in impact compared to control / usual standard care. Further, it should be noted that the research methodology (i.e. the systematic review process) employed for this thesis may not allow formal hypothesis testing to be carried out due to the expected variability between available studies in terms of intervention activities and endpoint measures. However, these hypotheses reflect the researcher's expectations based on theoretical roles and the background literature review.

3. Method

3.1 Inclusion Criteria

A comprehensive literature search was undertaken to identify randomised trials evaluating the impact of NP interventions delivering care through role substitution (RS) or through collaboration on interprofessional teams (IPTs). Trials were included if they met the following inclusion criteria:

- Randomised trial with randomisation at either the 1) individual level or 2) cluster level, only if there are multiple clusters (> or = 15 clusters / group) in both intervention and control groups.
- NP intervention implemented via either mode of role substitution (RS) or interprofessional team (IPT). All types of NPs were eligible, including PHCNP (Primary Health Care NP), ACNP (Acute Care NP), NNP (Neonatal NP), ARNP (Advanced Registered NP) etc. Context of program studies were included if the NP was the "+1" member of the intervention IPT, compared to an otherwise identical control IPT, or if the program was delivered exclusively by the NP(s).
- Intervention must be delivered in one of the following settings: primary health care, long term care, outpatient care (not admitted overnight to hospital) / specialized referral care, emergency department / acute inpatient hospital care.
- Risk of bias must be classified as low based on an assessment tool suggested by the Cochrane Collaboration[15] and adapted by Donald and colleagues.[38]
- Endpoint must be quantitatively measured within the following categories:
    - Death
    - Hospitalization (myocardial infarction / stroke / life-threatening event)
    - Treatment of a Chronic Disease (surrogate markers of disease may include physiologic markers e.g. blood glucose in diabetes; symptom severity e.g. post-operative symptoms in cardiac surgery outpatients; functional status e.g. peak flow in asthma patients; behaviour / lifestyle change e.g. diet in obese patients)
    - Drug Utilization (i.e. adherence or 'appropriate prescribing')
    - Resource Utilization (consultations, tests / investigations, referrals)
    - Cost
    - Quality of Life and / or Patient Satisfaction
    - Other

- Published in peer reviewed literature or grey literature, defined as reports produced by all levels of government, academics, business and industry in print and electronic formats but not controlled by commercial publishers.[15]
- Publication date of the study in the year 2000 or later.
- Study published in English.

Exclusion Criteria

Studies were excluded if they did not specify "nurse practitioner" as the sole nursing intervention. Examples of types of non-NP nursing professionals included:

- clinical nurse specialists
- community health nurses
- public health nurses

3.2 Literature Search Strategies

Grey literature was searched using (alphabetically): The Agency for Healthcare Research and Quality (AHRQ), The Canadian Electronic Library, The Canadian Nurses' Association, The Centre for Reviews and Dissemination, Center Watch, ClinicalTrials.gov, Grey Literature Report, Healthcare Standards Directory Online, the International Clinical Trials Registry Platform (ICTRP), The National Institute for Health and Care Excellence (NICE), The Ontario Health Technology Advisory Committee (OHTAC), Open Grey, ProQuest's Dissertations and Theses Databases, The Saskatchewan Registered Nurses' Association, and Turning Research into Practice (TRIP Database). Reference lists of relevant articles have been hand searched by the review author for potentially eligible studies.

The search strategy specific to Ovid MEDLINE (1973-April 2015) is outlined in Appendix F. The MEDLINE search strategy is a draft and was developed beginning with Ovid's Expert Search for randomized controlled trials (#1 - #23 from the search string in the appendix). Ovid MEDLINE identified 1,028,182 RCTs from 1973 – Present. This expert search feature is more effective than simply selecting the "randomized controlled trial" filter because it includes related studies and terms such as single blind methods, double blind methods, random allocations, etc. The draft strategy continues by broadly singling out nurse practitioners (NPs). The "Nurse Practitioner" Medical Subject Heading is restricted to records which list this term as a major topic of the research article. However, a wide range of keywords and synonyms accompany the subject heading. These include records which include "nurse practitioner" in the title of a record as well as records which contain the term at least twice in an abstract. A comprehensive list of search terms is available upon request.

On finalization, the search strategy from MEDLINE was translated, and used to search the Cumulative Index of Nursing and Allied Health Literature (CINAHL), PubMed, and EMBASE. Search terms included nurse practitioners, interdisciplinary patient care teams, interprofessional relations, nurse's role etc. Databases such as The Cochrane Central Register of Controlled Trials and Web of Science's Citation Index were also searched. However, these databases did not require search translations due to their varying interfaces and limited content compared to MEDLINE. The number of retrieved references were recorded and search strings for each database were saved. Searches can be re-run at any time. This data was managed in EndNote and included the amount of results from each database as well as the total amount of articles from each database (without duplicates). The publication date limit used in these searches was 1973 - present. Reference lists of relevant articles were hand searched by the review author for additional potentially eligible studies. Authors of relevant studies were contacted when necessary to clarify reported published information.

3.3 Review Process

The initial list of studies identified from the electronic search described above was de-duplicated prior to review. Next, two reviewers independently assessed the electronic citations (+ abstracts if applicable) using the relevance tool presented in Appendix A. Potentially relevant articles from the citation review underwent a full article review including a 'risk of bias' assessment. Agreement between assessors was measured by the kappa statistic.[15] Discrepancies between the two independent reviewers were resolved by a third person (D. Blackburn).

3.3.1 Validity Tool and Risk of Bias.

Risk of bias was assessed for all articles identified for the full-text review. Assessors used a tool adapted from the Cochrane collaboration[15] and from Donald and colleagues[38] [Appendix B]. The tool was designed to assess risk of bias across the domains of selection, detection, attrition, reporting, and all other concerns for bias not addressed in the previous domains. A judgement was assigned as either Yes (a low risk of bias), No (a high risk of bias), or Unclear (insufficient detail) by answering pre-specified questions. Overall, risk of bias was assigned to each study as follows: low risk of bias ("at risk" or "No" judgment in 0-1 category), moderate risk of bias ("at risk" or "No" judgment in 2-3 categories), high risk of bias ("at risk" or "No" judgment in 4-6 categories). The original Cochrane tool was modified following the justification of Donald and colleagues for the approach to NP interventions.[38] Specifically, the question about "blinding" was omitted from the tool because this convention is often impractical for NP intervention studies. Also, if outcomes had > 20 % missing data,

the study was judged to be at high risk of bias for "incomplete outcome data." After the validity assessment was completed by two independent reviewers, discrepancies were resolved by consensus, and any unresolved issues were resolved by a third person (D. Blackburn).

3.3.2 Data Extraction and Synthesis.

Studies that met all inclusion criteria underwent data extraction by LT using a standardized form developed and piloted for this specific study [Appendix C] prior to approval of protocol. Data extraction was cross-checked by NL prior to data synthesis.

Objective 1: to describe the types of activities that NPs have performed in randomised trials

All intervention activities undertaken by NPs in each study were described qualitatively within predefined categories derived primarily from the definition of the NP:[2] a) diagnosis b) prescribing pharmaceuticals, c) clinical procedures, and d) strategies for behaviour change / education. The additional category of e) care coordination was created by the review authors to categorize activities not accommodated by the original four categories. Diagnosis was defined as the identification of a disease or condition by a scientific evaluation of physical signs, symptoms, history, lab test results and procedures,[3] based on direct patient assessment, not withholding "diagnoses about higher levels of wellness."[9] In this review, diagnostic activities were divided into three sub-categories: open, limited, and diagnosis of disease status, with no evidence found of NPs diagnosing higher levels of wellness.

Open diagnoses were assigned if the NP diagnostic activities were unrestricted, and often involved 'ordering and interpreting diagnostic tests' (X-ray, organ function tests, blood tests, cultures etc.) and referring patients for specialty care. Limited diagnoses detected specific types of conditions, diseases, or risk factors for disease based on inclusion criteria, clinical protocols or clinical algorithms. Finally, 'diagnoses of disease status' were assigned when the NP intervention focused on patient populations who had previously been diagnosed with a specific disease. These diagnoses were thus restricted to the risk stratification of specific conditions, often guided by protocols or algorithms for the purposes of optimizing ongoing disease management or supporting patients' self-care.

Prescribing pharmaceuticals was defined as writing an order for a drug or treatment.[3] This activity was also sub-categorized by reviewers as open or limited. Open prescribing was assigned if the NP was responsible for all aspects of medication therapy. Limited prescribing often followed a protocol, restricted by condition or medication type. The domain 'clinical procedures' included administration of intra-muscular / intra-articular medications, application of stitches / dressings to wounds, thoracentesis or chest tube placement for pleural

effusion in cardiac surgery patients, or other clinical activities requiring direct manipulation of the patient (clean or sterile).

Education was defined as intellectual, moral and social instruction, giving information on a particular subject to improve knowledge.[11] Educational activities were classified separately from 'strategies for behaviour change', where NPs undertook an interactive process such as motivational interviewing, to increase patients' awareness of 'readiness to change,' for potential achievement of specific attainable goals related to a healthier lifestyle. In order to classify an activity as 'strategies for behaviour change', it had to be based on a psychological or cognitive model and delivered by NPs who received training in specific techniques.[12] Both activities of education and 'strategies for behavior change' could occur within a single study and ranged from providing a patient with written educational material, to face-to-face goal-setting for behaviour change based on psychosocial theory (e.g. motivational interviewing). Improved knowledge and behaviour change toward healthier lifestyles, in turn, support preventive healthcare that hinders the occurrence of an illness or decreases the incidence of a disease.[3] Three levels of prevention include: primary (aims to prevent disease or injury before it ever occurs) , secondary (aims to reduce the impact of a disease or injury that has already occurred, by detecting and treating disease or injury as soon as possible, to halt or slow its progress), and tertiary prevention (aims to soften the impact of an ongoing illness or injury that has lasting effects).[13] The final category of NP activity was termed 'care coordination.' Care coordination activities could not be classified within the traditional categories of diagnosis, prescribing, clinical procedures, or education / strategies for behaviour change. These interventions were typically delivered from a remote site via telephone or email and often required NPs to refer patients to appropriate services based on a limited assessment.

NP intervention activities were further organized by practice environment: primary health care, long term care, outpatient / specialized referral care, and emergency department / inpatient acute care; and by mode of NP implementation (RS or IPT), with an assessment made of the consistency of activities according to both setting and mode. Specifically, activities were grouped into the most common to least commonly undertaken in randomised trials. Ultimately, information on the types of activities undertaken in randomised trials was organized, synthesized and summarized in a clear and comprehensive fashion.

Objective 2: to describe the types of endpoints evaluated in RCTs examining the impact of NPs

The overall goal for objective two was to comprehensively describe the types of endpoints examined in NP intervention studies. All eight categories of quantitative endpoints in the review's inclusion criteria were broadly categorized into five categories for clarity of reporting: 1) clinical outcomes: death, hospitalization for life-threatening event; 2) surrogate measures of disease including: a) physiologic markers: e.g. blood glucose for diabetes status; b) i) symptom severity: e.g. post-operative symptoms related to cardiac surgery; ii) functional status: e.g. peak flow in asthma patients; and iii) behaviour / lifestyle change: e.g. diet and physical activity in obese patients; as well as c) drug utilization: e.g. medication compliance to lipid-lowering drugs in coronary heart disease patients; 3) resource utilization / cost; 4) overall quality of life / patient satisfaction; and 5) 'other.' Types of endpoints measured were reported with consideration of practice environment (i.e. primary health care, long term care, etc.) and mode of NP implementation (RS or IPT). The validity of each type of endpoint assessment was also examined and described. Overall, objective two resulted in a comprehensive description of the types of endpoints evaluated in NP intervention trials within each practice environment and each mode of NP implementation, with the quality / rigor of endpoint measurement also identified and described [Appendix I].

Objective 3: to describe the impact of NPs on all quantitative patient outcomes from randomised trials, conducting a meta-analysis to measure the impact of NPs on patient outcomes from homogeneous studies where possible

The impact of NP interventions on patient outcomes was descriptively reported for all studies. Although the 'ideal' goal of this research was to quantify the impact of NPs on patient outcomes, it was recognized that calculation of both summary effects and / or variance may not be possible if available trials do not assess these outcomes, or if existing articles are of poor quality. With careful attention paid to the similarity of outcomes, disease states, study duration and practice settings of all studies comprising this review, one pair of homogeneous studies contained quantitative data that was able to be pooled and meta-analyzed using *Comprehensive Meta-Analysis*.[39]

Amendments to the protocol were anticipated since the completion of a systematic review is an iterative process. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Appendix D) Statement acknowledges this iterative aspect of reviewing as necessary and appropriate within its guidelines for reporting systematic reviews.[40] The Preferred Reporting Items for Systematic Review and Meta-Analysis

Protocols (PRISMA-P; Appendix E) Statement, recently published in early 2015, provides a 17-item checklist to "facilitate the preparation and reporting of a robust protocol for the systematic review," further emphasizing the importance of transparency in the conduct and reporting of a systematic review.[14,41] Prior to screening for eligibility, the study protocol was registered on PROSPERO, an international prospective register of systematic reviews, publicly accessible with a Centre for Reviews and Dissemination (CRD) Number of 42015023509.[42] According to the PRISMA guidelines, modifications to the original protocol have been noted on PROSPERO.[43]

4.0 Results

4.1 Literature Search

A comprehensive literature search was performed using Ovid MEDLINE (1973-April, 2015). The search strategy from MEDLINE [Appendix F] was translated and used to search The Cumulative Index of Nursing and Allied Health Literature (CINAHL), PubMed, and EMBASE. The Cochrane Central Register of Controlled Trials and Web of Science's Citation Index were also searched; however, these databases did not require search translations due to their varying interfaces and limited content compared to MEDLINE. Searches were performed in April 2015 and were re-run for the first time in July 2015. Database searches identified 2142 citations: 274 citations from MEDLINE, 85 from CINAHL, 799 from PubMed, 394 from EMBASE, 462 from Web of Science, & 128 from Cochrane Central Register of Controlled Trials [Figure 1]. Forty additional citations were identified through searches in 15 different grey literature sites as well as one additional citation from hand searching relevant articles' reference lists.

4.2 Title and Abstract Review

In total, 2,183 citations were identified. Our team (LT, NL, and DB) agreed to limit articles to publication year 2000 instead of the original publication year of 1973, to ensure studies reflected contemporary health care and the current status of the NP role itself. Additional amendments prior to screening were to include 1) cluster randomised trials with > 15 clusters in each of the intervention and control groups, and 2) program studies, referring to RCTs that tested intervention programs either delivered by the NP(s) or a team of health professionals that may include a NP. Amendments to the original protocol were updated on PROSPERO.[42]

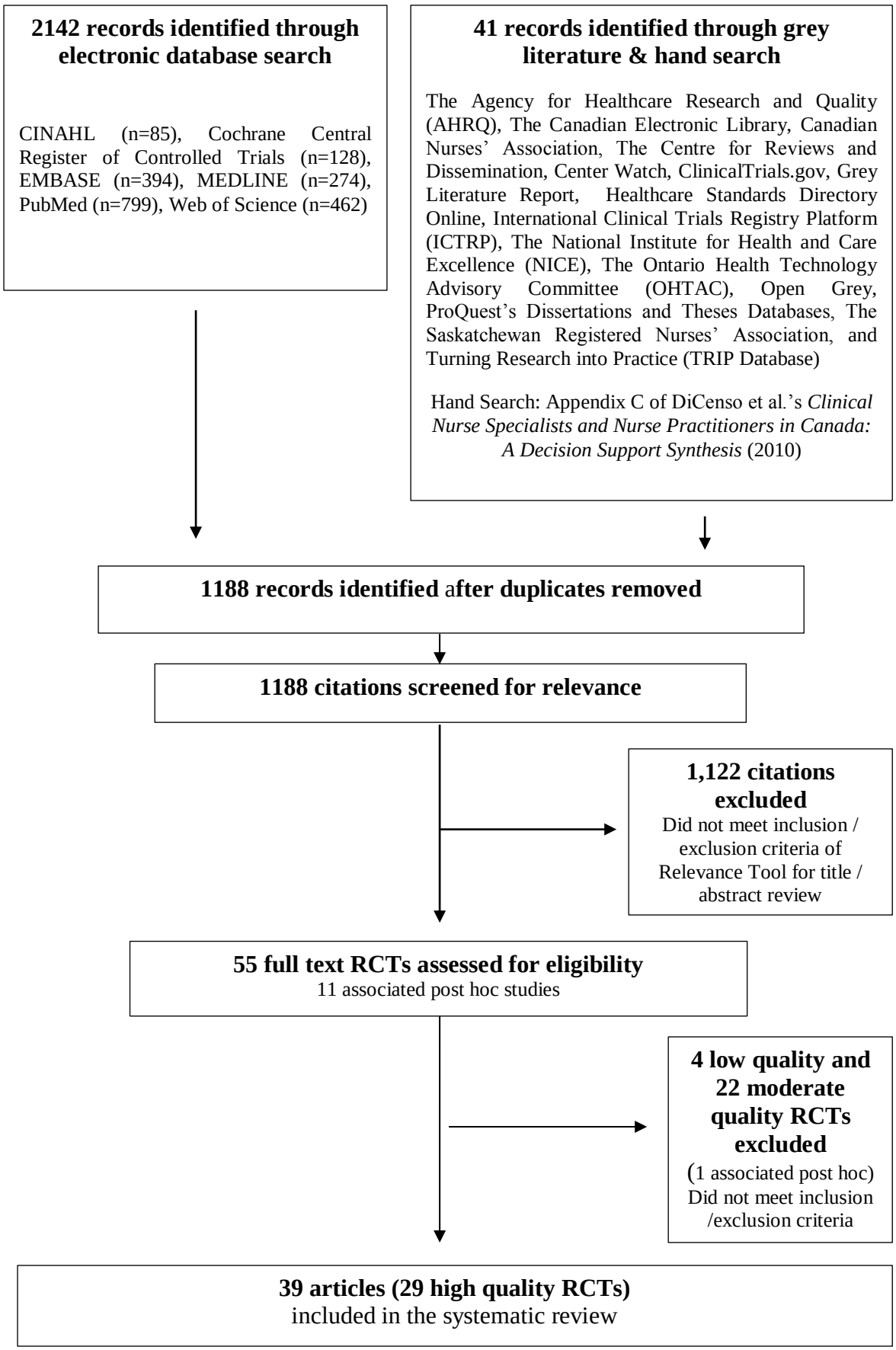
Following de-duplication, a total of 1,188 citations and abstracts were screened for relevance. Screening of citations and abstracts by two independent reviewers (LT and NL) according to Relevance Tool [Appendix A] resulted in an exclusion of 1,122 citations. Forty-nine articles were identified that did not clearly specify the type of APN (advanced practice nurse) credential of the nurse delivering the intervention (NP versus Clinical Nurse Specialist, or CNS). To seek clarification that the intervention be none other than a NP intervention, study authors of ambiguous APN articles were emailed. Five study authors replied with a "Yes" response to clarify that the APN intervention was delivered by a NP or NPs. Six authors replied to clarify that the APN intervention in nine different articles was delivered by a combination of APNs, such as NPs and clinical nurse specialists (CNSs). Four authors clarified that the intervention was delivered by only CNSs or "appropriately trained"

practice nurses. Remaining responses involved either a "bounce back" email that was apparently unreceived, a "No" response from the study author, or an absence of response. Database updates performed by the team's librarian (MH) in July 2015 resulted in 59 citations, all of which were redundant with the original set of search results except for one, which was an ambiguous APN article. The study author of this ambiguous APN article was emailed for clarification, but no response was received in return.

4.3 Full Text Review

A total of 55 RCTs underwent full text review using the Validity Tool [Appendix B]. Twenty-nine trials were assessed as high quality / low risk of bias [Appendix G; Figure 1], 22 were assessed as moderate quality (moderate risk of bias), and four were assessed as low quality (high risk of bias) studies [Appendix H; Figure 1]. A study with low risk of bias (zero 'at risk' or 'no' judgments) and two 'unclear' judgements was included in the review, with the arbitration acknowledging that a genuine unknown may not be penalized, in the context of otherwise sufficient information regarding trial conduct.[15] One of the originally included RCTs was recognized to contain a deficiency in criteria for inclusion, in terms of its lack of multiple clusters in each of the intervention and control groups. Upon agreement with the second independent reviewer (NL), this RCT was ultimately excluded from the review, resulting in a total of 39 articles (29 different RCTs) that underwent analysis of results [Appendix G; Figure 1]. Discrepancies between the two reviewers were resolved in all cases except for two studies assessed by a third reviewer (DB), resulting in their exclusion. Cohen's kappa for agreement between the two independent reviewers (LT and NL) was 0.78, reflecting excellent agreement.

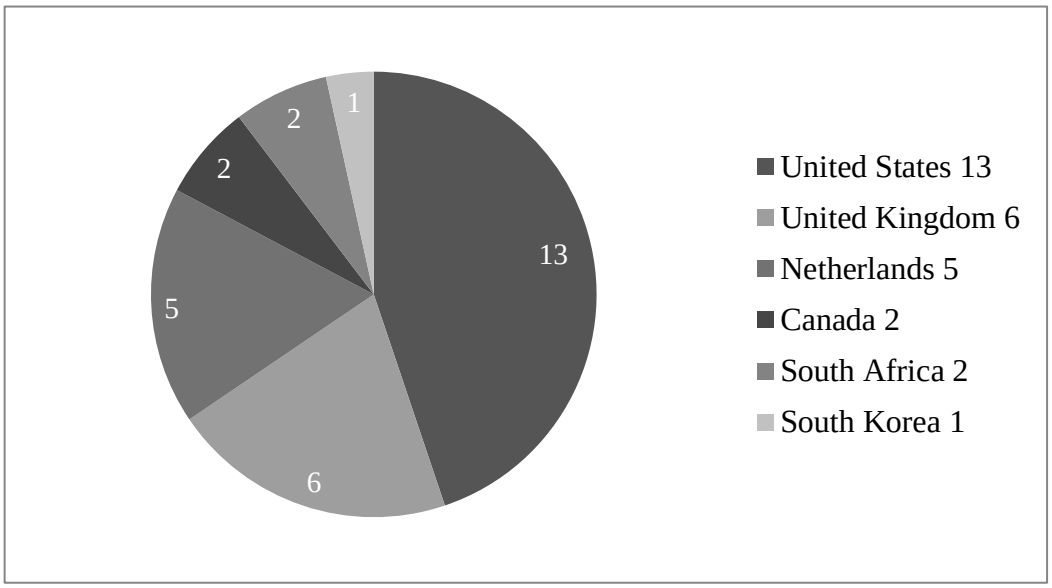
Figure 1 PRISMA flow diagram



4.4 Studies Meeting Inclusion Criteria

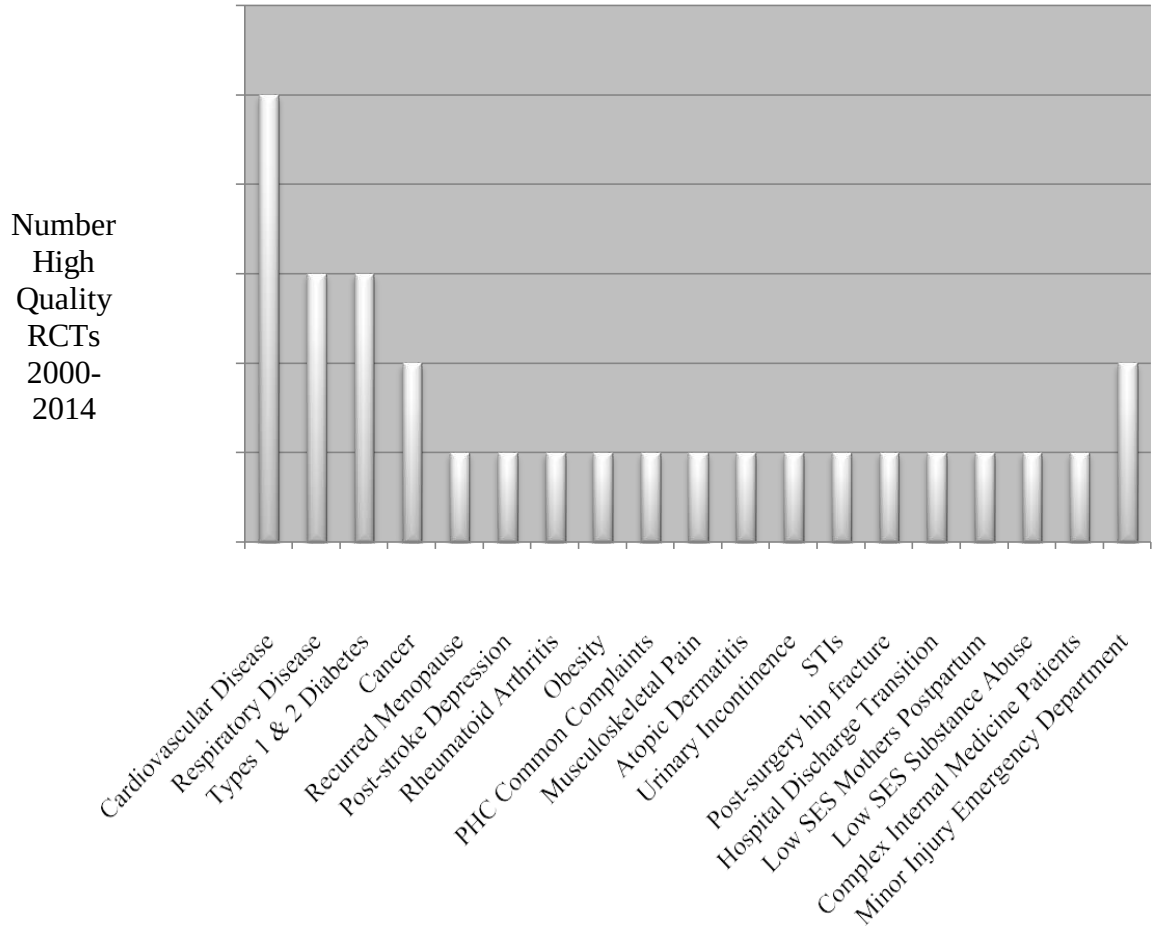
The 29 RCTs meeting all inclusion criteria originated from different countries in North America, Europe, Africa, and Asia [Figure 2]. All five trials from the Netherlands were published by unique authors / independent research groups.

Figure 2 Country of origin for 29 high quality RCTs examining NP interventions



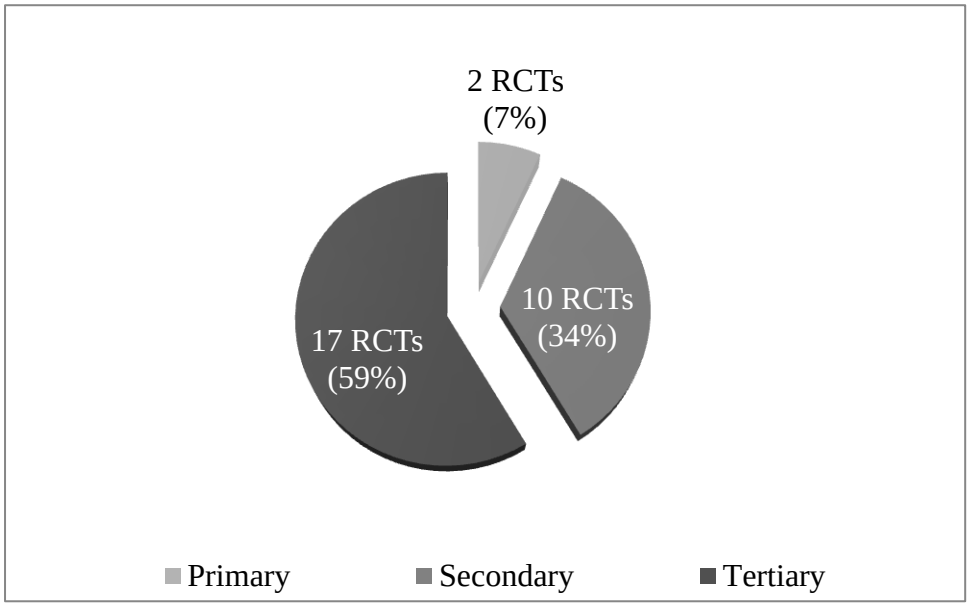
The majority of NP interventions addressed patients with chronic disease including: cardiovascular disease,[44-48] respiratory disease,[8,49,50] types one[7] and two[6,51] diabetes mellitus, cancer,[52,53] post-stroke depression,[54] rheumatoid arthritis,[55] and obesity[56] [Figure 3]. Obesity was recently classified by the Canadian Medical Association as a chronic disease,[57,58] a disease that significantly and directly links with many other chronic diseases.[56] Five trials were targeted to patients with specific conditions that are not, or may not be chronic / permanent: atopic dermatitis,[59] urinary incontinence,[60] menopause in breast cancer survivors,[61] and patients with minor injuries presenting to emergency department.[62,63] Two trials evaluated NP interventions for older adults post-hospitalization,[64,65] and several trials assessed the effect of NPs providing health care to patients in primary health care (PHC) settings: PHC clinics,[66,67] clinics within low socioeconomic populations,[8,68] patients' homes,[60,69] and college classrooms, where the study intervention aimed to improve knowledge of sexually transmitted infections (STIs) among female college students.[70] Only one trial tested an intervention in the acute inpatient environment, with NPs providing care to internal medicine patients[71] [Figure 3].

Figure 3 Health challenges studied in 29 RCTS



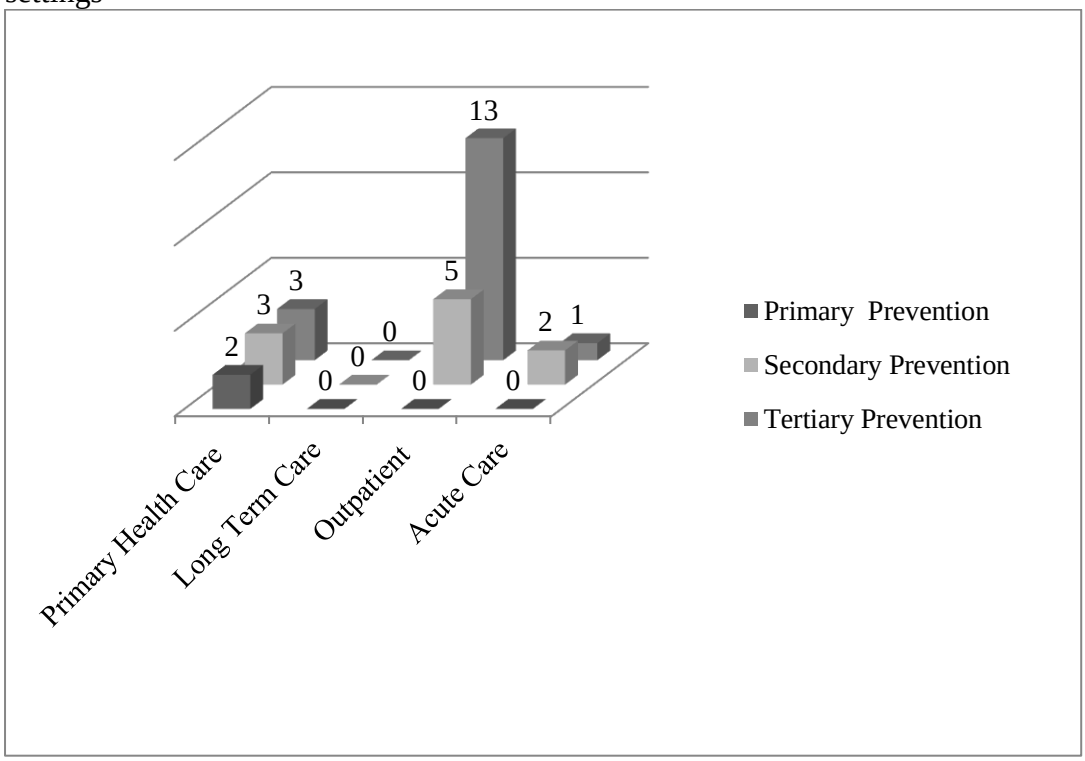
Trials that evaluated the effect of primary prevention interventions (preventing disease / injury before it ever occurs)[13] were found in two of the 29 (7%) studies.[69,70] Ten of the 29 trials (34%) tested a secondary prevention intervention (targeting disease / injury as soon as possible to halt or slow its progress).[13] The remainder of trials (17/29; 59%) measured patient outcomes that evaluated the effect of tertiary prevention interventions[13] (managing long-term, often complex health problems and injuries such as chronic diseases, permanent impairments) [6-8,44-51,53-55,66,68,71] [Figure 4]. Eight trials were based in primary health care settings [8,56,60,66-70] and eighteen were set in outpatient / specialized referral clinics;[6,7,44-55,59,61,64,65] only three [62,63,71] were set in acute care hospitals, with none set exclusively in long term care.

Figure 4 NP interventions in 29 studies stratified by three levels of prevention*



* Primary (1^0) - prevention of disease/injury before it occurs e.g. immunization, education on health/safety [3,13]
* Secondary (2^0) - early diagnosis, rapid initiation of treatment to halt or slow progress of disease/injury [3,13]
* Tertiary (3^0) - ongoing management of long-term, complex disease(s) / permanent injury e.g. rehabilitation for maximal recovery from permanent effects of cardiovascular events / permanent injury [3,13]

Figure 5 NP interventions in 29 studies stratified by three levels of prevention*and four settings



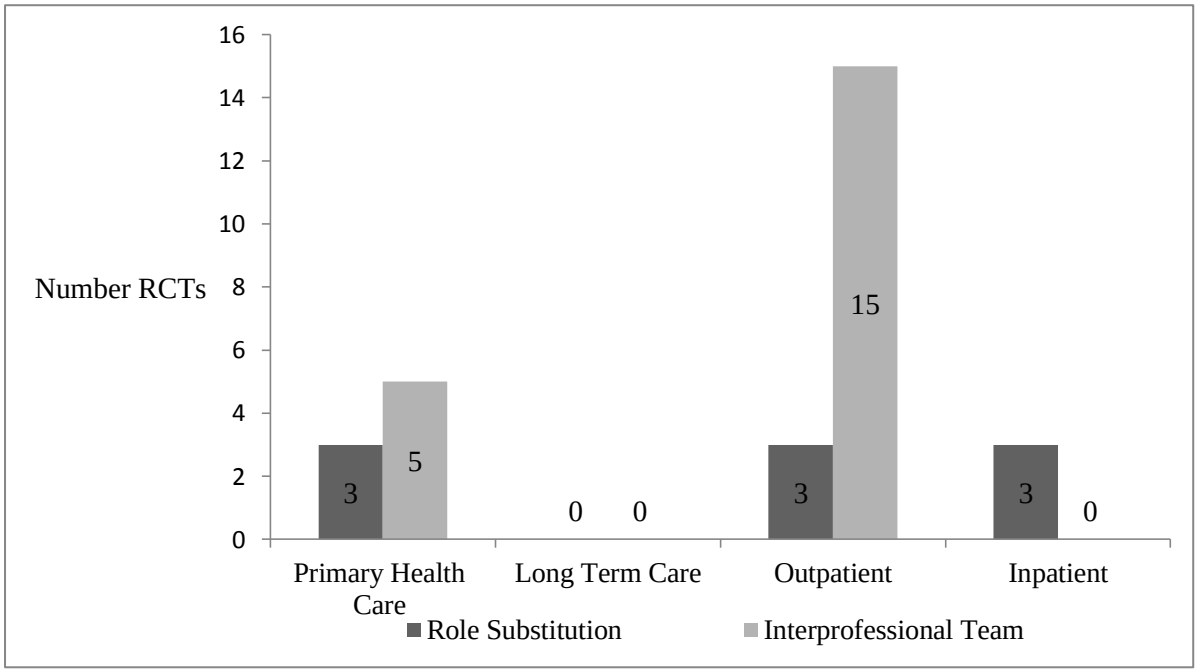
* Primary (1^0) - prevention of disease/injury before it occurs e.g. immunization, education on health/safety [3,13]
* Secondary (2^0) - early diagnosis, rapid initiation of treatment to halt or slow progress of disease/injury [3,13]
* Tertiary (3^0) - ongoing management of long-term, complex disease(s) / permanent injury e.g. rehabilitation for maximal recovery from permanent effects of cardiovascular events / permanent injury [3,13]

4.5 Objective 1. NP Intervention Activities Performed in RCTs

Overview:

The majority of RCTs in this review focused on the benefits of adding NPs to interprofessional teams (IPTs). Twenty out of 29 RCTs (69%) were classified as IPT trials.[6-8,44-48,50,51,53,54,60,61,64-66,68,70] The remaining nine RCTs were clearly designed to compare the effectiveness of an intervention delivered by a NP to another practitioner (i.e. role substitution).[49,55,56,59,62,63,67,69,71] Both role substitution (RS) and interprofessional team (IPT) trials were generally evenly spread across the timespan of this review. There are four RS trials published prior to 2009,[49,55,62,71] two published in 2009,[56,67] and three published after 2009.[59,63,69] Ten IPT trials were published prior to 2009 [61,44,66,45,46,8,60,47,64,70] three were published in 2009;[6,7,54] and seven were published after 2009. [51,,65,48,53,50,68] In RS trials, NP interventions were compared to standard care delivered by hospital-based professionals: extended scope physiotherapists, emergency room doctors, and medical house-staff; [62,63,71] general practice physicians (GPs);[56,67] and various specialists including rheumatology clinic physicians,[55] a respirologist,[49] a dermatologist,[72]and pediatricians.[69] Interestingly, all nine RS trials were evenly distributed across practice settings: three RS trials each in primary health care,[56,67,69] outpatient / specialized referral clinics,[49,55,59] and acute care[62,63,71] [Figure 6].

Figure 6 NP interventions in 29 studies stratified by mode of implementation* and setting



*Role Substitution (RS) - the NP acts as a replacement for another health care provider, and is delegated the responsibilities of diagnosing, prescribing, and overseeing patient care; relates to the origin of the NP role in Canada in 1973 to create alternative health care services where / when physician shortages were being experienced[5]

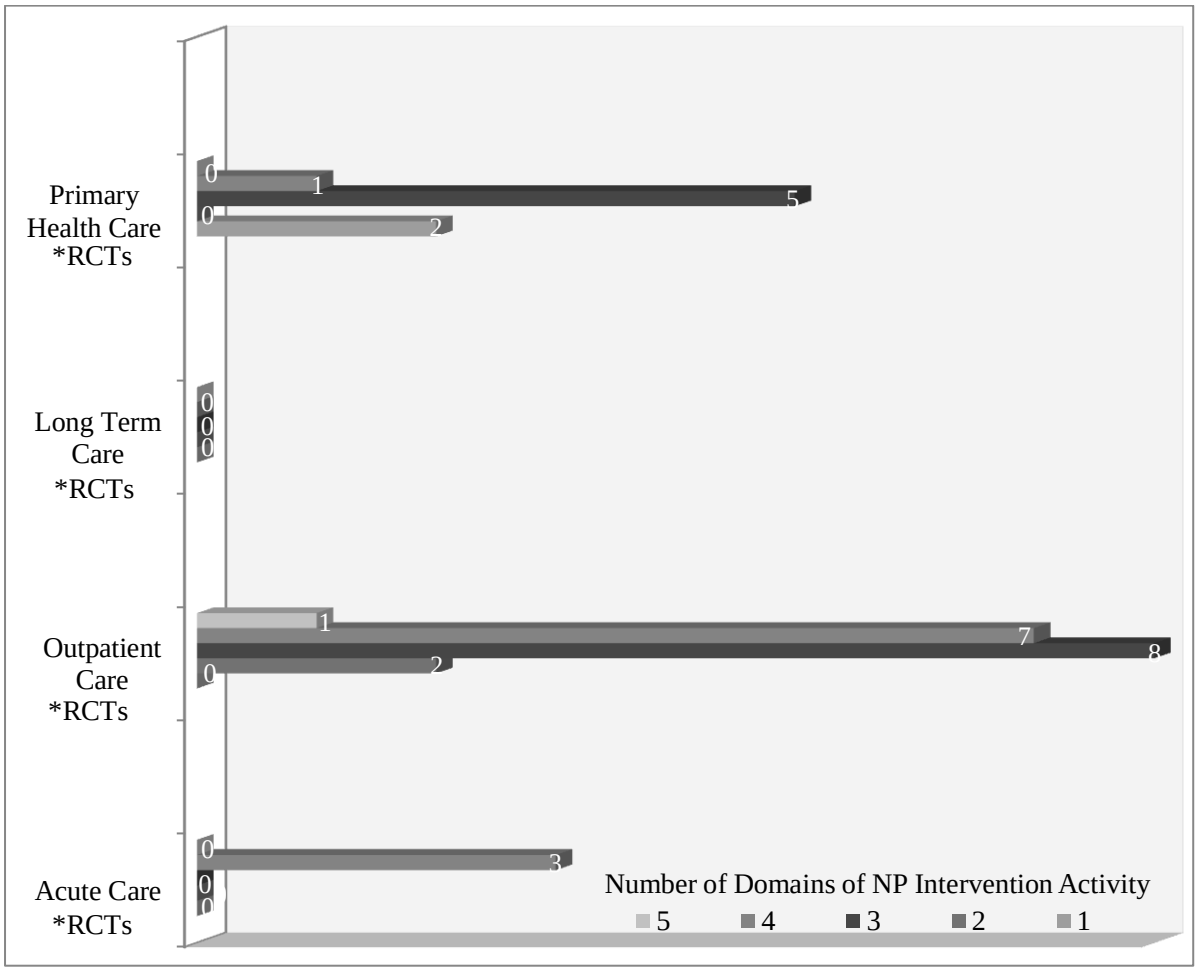
*Interprofessional Team (IPT) - the NP practices with at least one other health care provider to deliver patient/client care; IPT Study - mutually exclusive to a role substitution study

IPT trials were conducted in only primary health care [8,60,66,68,70] or outpatient / specialized referral clinics.[6,7,44-48,50-54,61,64,65] IPT interventions involved teamwork with professionals including: GPs and cardiac surgeons;[46,48] cardiologists;[44] general internists and cardiologists;[45] treating vascular specialists (vascular surgeon or neurologist);[47] pulmonologists;[50] other NPs;[8] pain clinic physician and other nursing specialists;[53] a Diabetes Care Center team for types one and two diabetes patients (physicians, NPs, on-site pharmacists, nurse educators, nutritionists, and mental health professionals);[6,7] a Diabetes Improvement Team for type two diabetes patients (physician, NP, registered dietician, and a diabetes nurse);[51] study psychiatrist;[54] psychiatric NP;[52] family and staff in various older adult facilities: primary physicians and hip surgeons;[64] medical and community services from the Health Maintenance Organization;[65] study physicians;[61] study conductors (educators);[70] continence NPs and continence advisory services (primary and hospital-based care);[60] and NPs trained in motivational interviewing for addiction, supported by community resources.[68] One RCT utilized the same single NP for delivery of care to both the intervention and control groups.[66] None of the RCTs tested their hypotheses exclusively within a long term care setting.

4.5.1 Five Domains of NP Intervention Activities

Activities delivered by NPs in each intervention were categorized into five domains: 'diagnosis,' 'prescribing pharmaceuticals,' 'clinical procedures,' 'strategies for behaviour change / education' and 'care coordination.' All five domains of activity were observed in one outpatient intervention delivered to cardiac surgery patients post-discharge.[48] Conversely, only one domain of activity was observed in two primary health care interventions: an educational lecture delivered to college students,[70] and a session of motivational interviewing provided to low socioeconomic patients at high risk for alcohol / drug use, to facilitate strategies for behaviour change.[68] All three acute care trials[62,63,71] contained all domains of intervention activity except for the off-site activity of care coordination [Figure 7]. Various combinations of domains were noted in the remaining 23 interventions. Activities most commonly performed by NP interventions were in the domain of 'education,' observed in all 29 RCTs. Strategies for behaviour change (which always included an educational component) were found in 13 RCTs. Diagnostic activities were performed in 27 RCTs, 'prescribing' in 20 RCTs, 'care coordination' in 11 RCTs, and 'clinical procedures' in five RCTs [Table 1].

Figure 7 Domains of activity in 29 NP interventions within different health care settings



* Randomised Controlled Trials (RCTs)

4.5.2 NP Interventions in Three Health Care Settings

As expected, the type of care delivered by NP interventions varied across settings. NP interventions in primary health care contrasted with those in acute emergency department / inpatient hospital settings, where the urgent immediacy of care in the latter setting was essentially opposite to that noted in primary healthcare. Although this observation is inherent to the settings themselves and not unique to NP interventions, what is notable in this review is the fact that all NP interventions performed in the outpatient / specialized referral setting were related to risk management of either chronic disease or older adults post-discharge to hospitalization, with the exception of two studies focussed on pediatric eczema[59] and abruptly recurred menopause in breast cancer survivors[61] [Table 1].

Table 1 Type of care delivered by NP interventions in 29 RCTs according to domains, settings and study populations (disease state / wellness[9])

	Primary Health Care,[3] including First-Contact Care[4] Clinic/Private Home/Classroom Health Care	**Outpatient / Specialized Referral Care[3]** Risk Management	**Emergency Department / Acute Inpatient Care[3]** Urgent Health Care
5 Domains		Coronary artery bypass graft surgery (Sawatsky[48] IPT^^: D,P,CP,E,CC) 3^0	
4 Domains	Obesity (ter Bogt[56] RS^: D,P,SBC,CC) 2^0	Coronary heart disease (Allen[44] IPT^^: D,P,SBC,CC) 3^0 Type 2 diabetes (Ralston[6] IPT^^: D,P,SBC,CC) 3^0 (Huizinga[51]IPT^^: D,P,SBC,CC) 3^0 Abdominal cancer (McCorkle[52] IPT^^: D,P,SBC,CC) 2^0 Advanced cancer (Kim[53] IPT^^: D,P,SBC,CC) 3^0 Rheumatoid arthritis (Hill[55] RS^: D,P,CP,SBC) 3^0 Older adults discharged from hospital (Enguidanos[65] IPT^^: D,P,E,CC) 2^0	Minor injury Emergency Department (Cooper[62] RS^: D,P,CP,E) 2^0 Soft tissue injury Emergency Department (McClellan[63] RS^: D,P,CP,E) 2^0 Internal medicine inpatients (Pioro[71] RS^: D,P,CP,E) 3^0
3 Domains	Maternal / infant health (Hannan[69] RS^: D,E,CC) 1^0 'Common complaints' (Dierick-van Daele[67] RS^: D,P,E) 2^0 Respiratory disease (Fairall[8]IPT^^: D,P,SBC) 3^0 Chronic musculoskeletal pain (Jones[66] IPT^^: D,P,E) 3^0 Incontinence (Williams[60]IPT^^: D,P,E) 2^0	Chronic heart failure (Ansari[45] IPT^^: D,P,E) 3^0 Cardiovascular surgery (Tranmer[46] IPT^^: D,E,CC) 3^0 COPD[+] (Berkhof[50]IPT^^: D,P,E) 3^0 Acute asthma (Nathan[49] RS^: D,P,E) 3^0 Hip fracture surgery (Krichbaum[64] IPT^^: D,P,SBC) 2^0 Type 1 diabetes (McCarrier[7] IPT^^: D,E,CC) 3^0 Atopic dermatitis (Schuttelaar[59] RS^: D,P,SBC) 2^0 Abruptly recurred menopause in breast cancer survivors (Ganz[61] IPT^^: D,P,SBC) 2^0	
2 Domains		Cardiovascular disease (Goessens[47] IPT^^: D,E) 3^0 Post-stroke depression (Mitchell[54] IPT^^: D,SBC) 3^0	
1 Domains	College education on sexually transmitted infection (Johnson-Mallard[70] IPT^^: E) 1^0 Addictions counselling (Mertens[68] IPT^^: SBC) 3^0		

1^0 Primary - prevention of disease/injury before it occurs e.g. immunization, education on health/safety [3,13]
2^0 Secondary - early diagnosis, rapid initiation of treatment to halt or slow progress of disease/injury [3,13]
3^0 Tertiary - ongoing management of long-term, complex disease(s)/permanent injury[3,13]
^Role Substitution (RS) ^^Interprofessional Team (IPT)
Domains: Diagnosis (D), Prescribing (P), Clinical Procedures (CP), Strategies for Behaviour Change (SBC), Education (E), Care Coordination (CC)
[+]Chronic Obstructive Pulmonary Disease (COPD)

4.5.3 Diagnosis

The vast majority of RCTs (27/29; 93%) involved some type of diagnostic activity within their intervention, including all of the role substitution (RS) trials (n = 9) and 90% (18/20) of the interprofessional team (IPT) trials. The most common diagnostic activities identified, related to diagnosis of disease status (i.e. ongoing assessment), observed in 59% (17/29) RCTs.[6,7,44-47,49-51,53-56,59,61,66,69] In approximately one third of the trials, (9/29 or 31%), the NP performed a limited diagnosis [8,48,52,60,62-65,67] while open diagnosis was observed in only one trial.[71]

The only intervention involving open diagnoses was based in a hospital setting where NPs were compared to medical house-staff in an internal medicine ward of a teaching hospital.[71] The NPs (2.5 full-time equivalent NPs) appeared to lead the clinical care of all patients in a specific 'NP ward,' with a medical director present at daily rounds and available for consultation. Patients in the 'house-staff ward' were managed by residents and interns that rotated every month, and were supervised by an attending doctor. In both the NP and house-staff wards, "ultimate responsibility for patient care rested with patients' attending doctors." However, NPs made clinical decisions with respect to patient management that previously had been performed by hospital physicians only. Thus, the intervention required NPs to independently diagnose and treat all patients assigned to their respective hospital ward.[71]

Interventions involving "limited diagnoses" were observed in nine RCTs. Although NP interventions focused on different types of patients across these studies, the nature of diagnostic activities were very similar in most cases, whether an IPT[8,48,52,60,64,65] or RS study design was used.[62,63,67] In general, patients presenting with certain conditions / symptoms were referred to NPs for ongoing management, including diagnoses of associated conditions. For example, in the RS study by Dierick-van Daele and colleagues, NPs were responsible for patients presenting with complaints common to a primary healthcare clinic, and performed relevant diagnoses pertaining to the initial complaint.[67] The specified set of common complaints compiled for this study included "respiratory and throat problems, ear and nose problems, musculoskeletal problems and injuries, skin injuries, urinary problems, gynaecological problems and geriatric problems."[67] In two other RS studies, emergency department patients with minor injuries that fell within the studies' protocols were assessed by NPs for specific diagnoses and subsequent management of the presenting problem.[62,63]

This approach to utilizing NPs for limited diagnostic activities was also applied within an IPT design to populations of low-income patients with respiratory illness,[8] to women with complications following abdominal surgery for suspected ovarian cancer,[52] and to outpatients

following coronary artery bypass graft (CABG) surgery.[48] For example, NPs assessed patients presenting with 'cough or difficult breathing' and subsequently diagnosed patients within a limited set of diseases: tuberculosis (TB), upper and lower tract respiratory infections, asthma, chronic obstructive pulmonary disease (COPD), and TB / HIV co-infection.[8] For women with suspected ovarian cancer, the NP monitored for post-surgical thromboembolism, infections and chemotherapy induced side- effects, with additional support available from a psychiatric NP team member who assessed women in significant emotional distress.[52] Post-discharge care of coronary artery bypass graft (CABG) surgery patients was provided by NPs who performed follow-up needs assessments by telephone, with additional care provided at an outpatient clinic if deemed necessary.[48] Specific diagnostic algorithms were not used in this process; rather individualized assessments by the NP determined the course of management required. Complex issues such as heart failure, wound infections, and pleural effusions were seen at the NP follow-up clinic and required longer NP follow-up care.[48]

Two IPT NP interventions focused on follow-up of older adults being discharged from hospital.[64,65] In the first RCT, the NP assessed medical needs of patients without existing support, using a checklist of "transition intervention activities," including psychosocial assessments.[65] The second RCT tested the effect of a mobile service model, to guide the NP in facilitating improved overall health, function, and return-home outcomes in older adults following hip fracture surgery.[64] Patients were followed by the NP for assessments of physical and psychosocial needs related to recovery from hip fracture surgery. This mobile service allowed the gerontologic NP to liaise between the patient, family and other health care providers.[64] Another mobile service was observed in an IPT trial that tested the impact of primary health care provided by continence NPs to patients in their own homes, with NPs diagnosing urinary tract infections or candida.[60] Of the nine RCT interventions employing limited diagnoses, the parameters of these activities were notably similar in both IPT and RS designs, by nature of the limited framework within which diagnosis took place.

The most common type of diagnostic activity identified in this systematic review was diagnosis of disease status, accounting for 63% of all NP interventions containing a diagnostic activity (17/27).[44-47,49,55,56,61,66,69, 6,7,50,51,53,54,59] Of these, the majority of interventions focused on the management of chronic diseases such as medication titration in patients with diabetes mellitus,[6,7,51] management of hypercholesterolemia in coronary heart disease,[44] use of beta-blocker medication in chronic heart failure,[45] and management of chronic pain in patients with advanced cancer.[53] Other chronic diseases managed by NPs

included chronic obstructive pulmonary disease (COPD),[50] rheumatoid arthritis,[55] asthma,[49] and obesity.[56] An example of NPs performing 'diagnosis of disease status' in the context of chronic disease management is found in the IPT trial by Goessens and colleagues.[47] NPs tracked status of cardiovascular risk factors such as blood pressure and cholesterol in outpatients with various vascular diseases and directed management based on these ongoing assessments.[47] In a RS trial by Nathan and colleagues, NPs followed-up with patients recently discharged from the hospital to monitor status of acute asthma exacerbations, peak flow measurements and other asthma symptoms, titrating medications (inhaled / oral corticosteroids) and readmitting acute asthma patients to hospital as required.[49] Diagnosis of disease status was observed in another outpatient trial that focused on pediatric patients with mild, moderate and severe atopic dermatitis (eczema). The NP performed an exam of the skin and diagnosed particular allergies related to food, inhalants, or serum-specific immunoglobulin E allergens.[59]

4.5.4 Prescribing Pharmaceuticals

Prescribing pharmaceuticals, or 'writing orders for drugs or treatments,[3] occurred in 20/29 (69%) of the RCTs. Open prescribing occurred in only one trial, the same trial that involved open diagnosis, where the NP managed all patients in an internal medicine ward of a teaching hospital.[71] Changes in the availability of medical residents in 1989 led this hospital to create a ward staffed by NPs, at which time the NP role expanded from care of patients with chronic well-circumscribed illnesses (e.g. patients requiring prolonged courses of intravenous antibiotics) to care of general medical patients with acute medical conditions.[71]

Nineteen trials included limited prescribing as part of the NP intervention. Limited prescribing varied across a wide spectrum of discretion, including prescribing for multiple conditions / risk factors,[8,48,52,56,60,62,63,67] prescribing for a single condition/risk factor,[6,44,45,49-51,53,55,59,61,66] and prescribing within one particular drug class (non-steroidal anti-inflammatory drugs or NSAIDs).[66] In some RCTs, investigators indicated that the scope of prescribing activities might have been greater if not for restrictive legislation in Europe[47,67] and the U.S.[64] The majority of limited prescribing activities occurred in the context of tertiary prevention / chronic disease management (11/19 RCTs or 58%),[6,8,44,45,48-51,53,55,66] with the remainder of prescribing activity occurring in secondary prevention RCTs.[52,56,59-63,67] For example, NPs were responsible for titration of lipid-lowering medications in coronary heart disease patients,[44] beta-blockers in patients with chronic heart failure,[45] anti-hyperglycemic medications in patients with type two diabetes mellitus,[6,51] and respiratory medications for patients with acute asthma.[49] In terms of secondary prevention, dermatologic therapies were

prescribed by NPs for children with atopic dermatitis (eczema),[59] as were medications / supplies for patients with incontinence.[60] In a trial originating from a women's health clinic for breast cancer survivors, NP prescribing was limited to the occurrence of distressing menopausal symptoms on discontinuation of estrogen replacement therapy.[61] The most limited prescribing intervention was observed in a trial by Jones and colleagues, where the NP was solely focused on the reduction or discontinuation of over-the-counter non-steroidal anti-inflammatory drug (NSAID) use in patients with non-malignant, non-inflammatory musculoskeletal pain, particularly in the elderly with osteoarthritis.[66]

However, other interventions involved limited prescribing in a less restricted setting. For example, in the cluster RCT by Fairall and colleagues,[8] the NP managed patients with a variety of respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), tuberculosis (TB), lower / upper respiratory tract infections, and TB-HIV co-infection. These NPs were granted authority to prescribe inhaled corticosteroids for asthma, short course oral corticosteroids for exacerbations of obstructive lung disease, and cotrimoxazole prophylaxis for symptomatic HIV infection.[8] Prescribing of pain medication was performed in two trials involving cancer patients,[52,53]and in one trial of coronary artery bypass graft (CABG) outpatients, for whom alternate analgesics were prescribed as necessary.[48] Self-adjustment of pain medication was taught to patients with advanced cancer, with an appropriate dosage recommended by a NP to each patient according to an algorithm for pain control.[53] Collaborative prescribing plans were developed by NPs managing patients on their return home following abdominal surgery that may have entailed oophorectomy / hysterectomy. A psychiatric NP developed a collaborative prescribing plan with an oncology NP who monitored post-operative stabilization of patients and monitored chemotherapy side-effects.[52]

Limited prescribing was also performed in RCTs targeting patients with acute conditions. For example, NPs in emergency room settings managed patients with a variety of minor injuries.[62,63] Although specific prescribing activities were not described in one of these two study methods, it was assumed limited prescribing occurred since the NP intervention was compared to emergency department doctors through a RS design.[62] In the other RCT evaluating NPs in an emergency room setting, limited NP prescribing was clearly evident, and compared to that of extended scope physiotherapists and emergency room doctors, with NPs prescribing to 23.2% of their patients, ESPs to 3.6% of their patients, and doctors to 42.2% of their patients.[63] Finally, NPs performed medication reviews in two trials of older adult patients discharged from overnight stays in hospital.[65,64] Medication assessment was

performed by the NP for the purposes of medication reconciliation, where any discrepancy in medication regimens between admission and discharge of care facilities was identified and resolved, discontinuing and writing new prescriptions when necessary.[73]

4.5.5 Clinical Procedures

Of the 29 RCTs identified in this review, five (17%) included clinical procedures as part of the intervention.[48,55,62,63,71] Three of these interventions were situated in a hospital setting[62,63,71] where NPs performed procedures on patients presenting to emergency departments [62,63] or to patients receiving care in an internal medicine ward.[71] In each of these three trials, the actual clinical procedures were not explicitly described in the study methods. However, the reviewers assumed clinical procedures were performed based on the nature of the intervention described. For example, in two of these trials, NPs provided care to patients presenting with minor injuries in the emergency department.[62,63] NPs were responsible for the diagnosis and treatment of minor injuries such as sprains, burns, contusions, fractures, and minor head injuries. Thus, the performance of clinical procedures such as wound dressings, closed reduction of fractured bone, and application of splints and stitches were highly probable given the nature of the NP's role in these studies.[62,63] Similarly, in a study by Pioro and colleagues, NPs were responsible for the care of all patients admitted to an internal medicine ward with issues related to gastrointestinal, pulmonary, infectious, metabolic, neurological, cardiovascular and "other" conditions including substance abuse.[71] Again, clinical procedures were not explicitly documented. However, the reviewers assumed these activities were performed by the NP given the broad scope of this intervention.[71]

The final two interventions involved clinical procedures in outpatient settings, examining the effectiveness of NP-led care for rheumatoid arthritis patients,[55] and the effectiveness of NP follow-up care for newly discharged coronary artery bypass graft (CABG) patients.[48] In the former trial, NPs were responsible for virtually all aspects of patient care in an outpatient setting (i.e. assessment, disease management, recommendations to rheumatologists / GPs regarding therapy, referrals, and counseling), including the administration of intra-articular or intra-muscular steroids when clinically indicated.[55] In the latter trial, approximately 25% of the intervention group participants were seen in a NP follow-up clinic for complex cardiac surgery-related issues, such as heart failure, wound infections, and pleural effusions, potentially requiring thoracentesis for drainage and / or chest tube placement for continuous drainage.[48]

4.5.6 Strategies for Behaviour Change / Education

All of the NP interventions identified in this review included some type of educational or behaviour change activity. Strategies for behaviour change always included an educational component and were part of the NP intervention in 13/29 (45%) original RCTs.[6,8,44,51-56,59,61,64,68] A good example of a behaviour change intervention was observed in the study by Mertens and colleagues.[68] Primary care NPs were given a three-day training session in Brief Motivational Interviewing, based on *Rollnick's Health Behavior Change: A Guide for Practitioners.*[74] To maintain fidelity to the Brief Motivational Interviewing model, NP training was followed by regular supervision meetings (weekly for six weeks and monthly thereafter), during which time NPs listened to recordings of their interventions with their trainer. This trial tested the effectiveness of a brief motivational interviewing intervention (average duration 10 minutes) on reduction of high-risk alcohol and drug use in young adult primary care patients from a low-income population and country.[68] Other RCTs described behaviour change interventions ranging from specific lifestyle modifications [6,8,44,51,56] to management of fatigue,[55] pain,[53] menopausal symptoms in breast cancer survivors,[61] post-stroke depression,[54] coping with childhood illness[59] and post-operative recovery[52,64] [Table 2].

Table 2 Behaviour change strategies conducted by NP interventions in 13 RCTs

Lifestyle modifications

Allen[44]
NP case management by 'tailored lifestyle & medication intervention + enhanced usual care,' with counseling for lifestyle modifications in diet, physical activity, & smoking cessation; 1 year intervention post-discharge, in outpatients who received coronary artery bypass grafting (CABG) surgery or percutaneous coronary intervention

Sol[75] **(post hoc to Goessens**[47]**)**
'NP at risk factor management clinic + usual care' for cardiovascular disease outpatients; 12 month intervention where patients' motivation for achieving behavioural change was assessed; goals were set toward behavioural change in context of self-efficacy promotion

Fairall[8]
'Practical Approach to Lung Health in South Africa (PALSA) Intervention,' an educational outreach program implemented by NPs including counseling for smoking cessation, for patients with cough or difficult breathing on presentation / within last six months; 3 month study period at 20 primary health care clinics

Ralston[6]
'NP coordination of Web-based care + usual care,' for reduction of blood glucose in Type 2 Diabetes Mellitus patients, with counseling to guide health behaviour change according to Wagner's Chronic Care Model; 12 month intervention

ter Bogt[56]
Low-intensity (to prevent additional weight gain) lifestyle counseling by NPs: 4 individual visits and 1 feedback session by telephone over 1 year patients with BMI 25- 40, and either hypertension, dyslipidemia or both

Huizinga[51]
'Usual care + NP phone contact (quarterly and monthly)' over 2 years for prevention of glycemic relapse (defined as an increase in HbA1c of > or = to 1% over baseline) in Type 2 Diabetes Mellitus patients. Intervention included identification of problems arising in self-care behaviours, anticipatory planning and motivational interviewing for achievement of mutually established goals

Psychosocial Management of Pain and Fatigue

Kim[53]
'Usual care + daily phone monitoring (tele-monitoring)' by NP for advanced cancer outpatients diagnosed with stage IV solid tumor, moderate level of cancer-related pain (Visual Analog Scale score ≥4 out of 10 over last 24 h), and life expectancy >1 month; psychosocial pain management intervention for 1 week

Hill[55]
'Rheumatology NP (RNP) care' including psychosocial management of fatigue in rheumatology outpatients; study period 12 months

Psychosocial Management of Abruptly Recurred Symptoms

Ganz[61]
'Comprehensive menopausal assessment' targeting highly symptomatic women with the goal of reducing symptoms & improving quality of life, through education, counseling (including behavioral interventions, psychosocial support), & focused 'non- estrogen replacement therapy' interventions; delivered by NP to breast cancer survivors for 4 months

Reduction in High-Risk Addiction Behaviour

Mertens[68]
'Single session of Brief Motivational Interviewing (average session 10 minutes) delivered by NP + referral list of support resources,' in patients 18–24 years screened for high-risk alcohol and / or drug use; study period 3 months

Post-Stroke Depression

Mitchell[54]
'Brief psycho-social/behavioural intervention (9 in-person sessions with NP over 8 weeks) + usual care,' alongside antidepressant medication in outpatients within 4 months of an ischemic stroke; 8 week intervention within a 24 month study period

Coaching Support for Parents of Children with Eczema

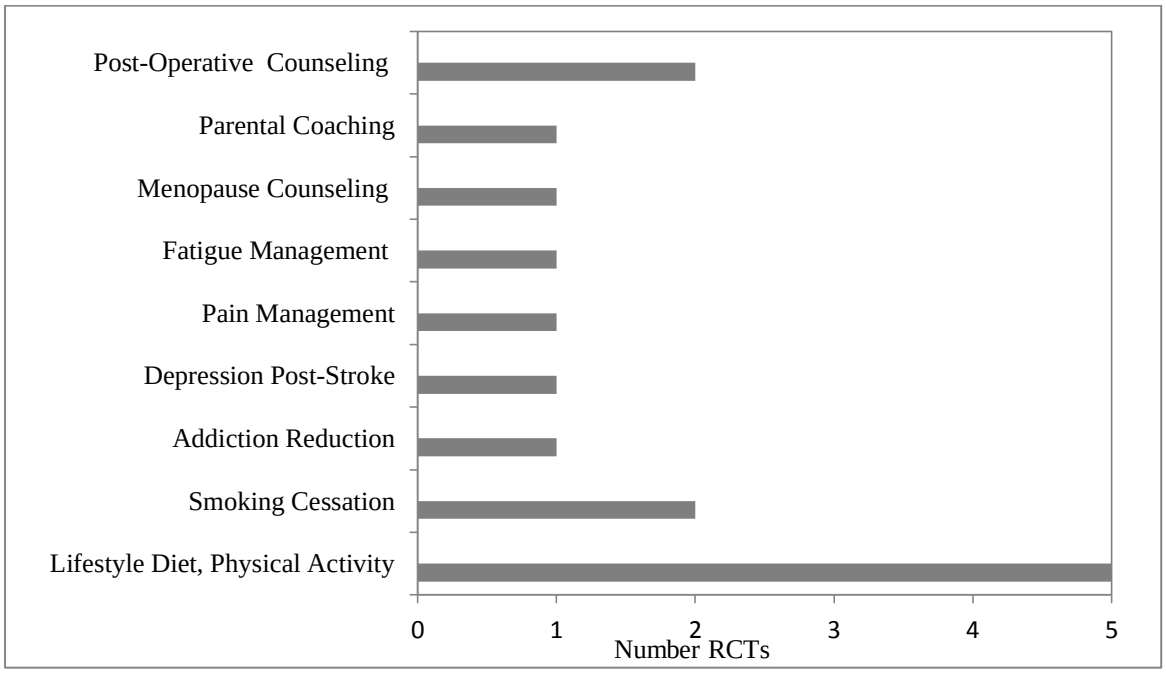
Schuttelaar[59]
NP-led care in outpatients < 16 years, referred by GPs or pediatricians with a diagnosis of eczema; 1 year study with intervention including application of social cognitive theory (Bandura) that identifies factors influencing self-management: self-efficacy, behavioural capability (knowledge and skills) & outcome expectations. The NP intervention reinforced belief in the parents' own abilities with regards to controlling their child's eczema, by teaching and counselling parents

Post-Operative Counseling Support

Krichbaum[64]
'Usual care + post-acute care coordination' by gerontologic NP for hip fracture surgery outpatients; 6 month intervention, including counseling older adult clients in a 12 month study period

McCorkle[52]
18 contacts by an oncology NP during the first 6 months after hospital discharge, to assist surgical outpatients with suspected primary diagnosis of ovarian cancer in developing & maintaining self-management skills of physical & psychosocial health, through counseling of patient and family caregiver; supplemented by psychiatric NP consults if warranted; 6 month study duration

Figure 8 Frequency of strategies for behaviour change in NP interventions from 13 RCTs



A multifaceted intervention involving educational and lifestyle / behaviour change activities was observed in a web-based intervention for patients with type two diabetes.[6] The NP facilitated behaviour change, providing strategies according to Wagner's Chronic Care Model,[76] comprised of four essential health system elements for high-quality chronic disease care: self-management, decision support, delivery system design, and clinical information systems. Following an initial one-hour consultation consisting of problem identification, goal setting, and skill development, ongoing patient education occurred through an interactive web-based tool focused on nutrition, medications, and exercise. Patients electronically submitted blood glucose readings and communicated regularly with the NP through secure e-mail.[6]

Traditional educational activities alone, without a behaviour change component, were provided by the NP in 16/29 (55%) RCTs,[7,45-50,60,62,63,65-67,69-71] either: over the phone,[46,48,65,69] face-to-face (i.e. in a hospital,[62,63,71] an office,[45,47,49,50,66,67] classroom,[70] or the patient's home[60,65,66]), or via written material (leaflets [45,60,66,69,70] or an electronic platform [6,7]). Education was delivered to individuals, families[69] or groups.[70] In one trial, education served as the sole activity of the NP intervention. In this case, the NP intervention was an educational lecture about sexually transmitted infections (STIs) to a group of female college students of child-bearing age, to potentially reduce knowledge gaps related to STI morbidity associated with reproductive health: chronic pelvic pain, pelvic inflammatory disease, infertility, ectopic pregnancy, compromised birth outcomes, and cervical cancer.[70] A trial

testing an intervention on maternal / infant health in mothers and infants with good health at baseline, involved NPs phoning post-partum mothers on six occasions to provide education and screen for health concerns.[69]

In most RCTs, NP education was one component of a multifaceted intervention. Trials varied with respect to the amount of detail provided about educational activities; however, patient knowledge, attitudes, and / or beliefs were clearly prioritized in virtually all trials. For example, in a RCT evaluating specialized outpatient services for older adults, education was provided to reinforce discharge teaching (self-management of target symptoms and side-effects).[65] Less detail was provided in the emergency department trials, although teaching on discharge was assumed to have taken place as an essential standard of care.[62,63] More detail is found in an intervention focusing on patients with incontinence problems, where NP's provided education on non-pharmacologic management including healthy eating / fluid intake, bladder training, and pelvic floor awareness in addition to physical examinations, diagnostic assessment, and prescribing.[60] Education activities within multifaceted interventions often included teaching self-management skills.

Self-management teaching was most commonly observed in interventions for chronic disease management.[7,46,47,49,50,66] For example, patients were engaged in creating plans of self-care to manage chronic musculoskeletal pain,[66] to self-monitor and respond to symptoms of chronic obstructive pulmonary disease,[50] and to alter lifestyle for management of cardiovascular risk factors[47] as well as type one diabetes mellitus.[7] Similar to the web-based study of type two diabetes patients, education from an NP was delivered to patients with type one diabetes via a web-based platform that included a daily "diabetes diary," an "action planner", and a portal providing patients with an array of diabetes related information, for ongoing updates to their learning and self-management.[7] Whether primary,[70] secondary,[60,65] or tertiary prevention,[7,46,47,49,50,66] self-management teaching was most prevalent in NP interventions that facilitated patients' long term management of tertiary level, irreversible chronic disease.

4.5.7 Care Coordination

Care coordination involved activities that could not be completely classified within the traditional categories of diagnosis, prescribing, clinical procedures, or strategies for behaviour change / education. As already noted in the previous four domains, the 11 interventions classified in this domain[6,7,44,46,48,51-53,56,65,69] do include varying degrees of activity in the traditional categories, but in many cases, these were largely achieved offsite, and lacked in-person contact between NPs and patients. Care coordination activities were

delivered from a remote site via telephone or email and often, required NPs to refer patients to appropriate services based on a limited assessment. NPs coordinated with patients via the phone in nine RCTs.[44,46,48,51-53,56,65,69] In four of these nine trials, NPs implemented their intervention completely via phone.[46,51,53,69] Two trials implemented their NP intervention primarily via email.[6,7]

An example of a care coordination activity completed exclusively via phone was conducted in a population of outpatients recently discharged after cardiac surgery.[46] NP phone sessions provided ongoing information and assessment, assisted with self-management of common symptoms, and facilitated referrals to appropriate health care resources for resolution of some of the presenting problems.[46] Patient care algorithms related to chest pain, gastrointestinal disturbances, infection, leg swelling, shortness of breath, and sleep pattern disturbances were developed and approved by an interdisciplinary joint practice committee, and were used as guidelines for the provision of care.[46] Similarly, a NP intervention for postpartum mothers and newborns was delivered completely by telephone. NPs collected information and referred patients as appropriate to their primary care physician or even 911 emergency services based on the verbal interview.[69] For patients with type two diabetes mellitus, NPs implemented their intervention completely via phone, although intervention protocols and guidelines occasionally entailed coordinating with the study dietician.[51] In a study of advanced cancer patients, following an in-person 30 minute standardized education session in a pain clinic, pain management for these patients was subsequently coordinated exclusively by the NP via phone.[53]

Care coordination of patients discharged after a coronary artery bypass graft (CABG) surgery, entailed initial screening by the NP via telephone, who then directed patients to either follow-up with their primary care provider, the cardiac surgeon, the emergency department; or to receive further monitoring by the NP, which was provided by a subsequent telephone call or an in-person appointment at the NP follow-up clinic.[48] A combination of phone, home visits, and clinic appointments was also utilized for a NP intervention delivered in the post-operative period to women with suspected ovarian cancer.[52] Phone contact was an adjunct to in-person care in a study that measured the effectiveness of NP care in hyperlipidemia management for coronary heart disease patients. The phone activity allowed the NP to coordinate with the patient for the purposes of adjusting appropriate lipid-lowering medications on the basis of the results of follow-up blood tests, and for reinforcement of lifestyle counseling.[44] Most of the interventions employing care-coordination activities were focused on assisting patients in developing and maintaining self-management skills, to

facilitate patients' active participation in treatment decisions, and to monitor and manage patients' physical and psychological health.[52,65]

Email was used as the primary mode of communication for two NP interventions focusing on patients with diabetes mellitus.[7,6] In both RCTs, an initial in-person, one-hour consultation conducted by the NP was followed by subsequent implementation of web-based modules designed to improve diabetes self-care. The NP provided feedback in both studies to patients' uploaded information (both patient and provider were able to view the trended displays of blood glucose readings, and data entries for medication, nutrition, and exercise) and to patients' correspondence via email.[6,7] Information on the types of NP intervention activities undertaken in randomised trials, from the most to least commonly undertaken, was organized by practice setting and mode of NP implementation, with an assessment of the consistency of activities according to both setting and mode [Table 3].

Table 3 Distribution of NP intervention activities by setting and mode

NP Intervention Activities	**Diagnosis**	**Prescribing**	**Clinical Procedures**	**Education / Strategies for Behaviour Change**		**Care Coordina-tion**
TOTAL 29 RCTs*	**27 RCTs***	**20 RCTs***	**5 RCTs***	**Education Only /** **16 RCTs***	**Behavior Change Strategies,** including education **13 RCTs***	**11 RCTs***
PHC** 8 RCTs*	**75%** 6/8 RCTs	**63%** 5/8 RCTs	**0%** 0/8 RCTs	**62.5%** 5/8 RCTs	**37.5%** 3/8 RCTs	**25%** 2/8 RCTs
LONG TERM CARE 0 RCTs*	**0%** 0/0 RCTs	**0%** 0/0 RCTs	**0%** 0/0 RCTs	**0%** 0/0 RCTs		**0%** 0/0 RCTs
OUTPATIENT/ Specialized Referral 18 RCTs*	**100%** 18/18 RCTs	**67%** 12/18 RCTs	**11%** 2/18 RCTs	**44%** 8/18 RCTs	**56%** 10/18 RCTs	**50%** 9/18 RCTs
ACUTE INPATIENT 3 RCTs*	**100%** 3/3 RCTs	**100%** 3/3 RCTs	**100%** 3/3 RCTs	**100%** 3/3 RCTs	**0%** 0/3 RCTs	**0%** 0/3 RCTs
NP Intervention Activities	**Diagnosis**	**Prescribing**	**Clinical Procedures**	**Education / Strategies for Behaviour Change**		**Care Coordina-tion**
RS^ Mode 9 RCTs*	**9/9:** 3 Acute, 3 Outpatient, 3 PHC**	**8/9:** 3 Acute, 3 Outpatient, 2 PHC**	**4/9:** 3 Acute, 1 Outpatient	**6/9:** 3 Acute, 1 Outpatient, 2 PHC**	**3/9:** 2 Outpatient, 1 PHC**	**2/9:** 2 PHC**
IPT^^ Mode 20 RCTs*	**18/20:** 15 Outpatient, 3 PHC**	**12/20:** 9 Outpatient, 3 PHC**	**1/20:** 1 Outpatient	**10/20:** 7 Outpatient, 3 PHC**	**10/20:** 8 Outpatient, 2 PHC**	**9/20:** 9 Outpatient

* Randomised Controlled Trials (RCTs) ** Primary Health Care (PHC)
^Role Substitution (RS) ^^Interprofessional Team (IPT)

4.6 Objectives 2 and 3. Quantitative Endpoints and Impact on Patient Outcomes

Overview:

The impact of 29 NP interventions was assessed through various study endpoints relating to a) clinical outcomes (life-threatening events and death); b) surrogate measures of disease (physiologic markers, 'symptom severity, functional status, behaviour / lifestyle change,' and drug utilization); c) resource utilization / cost; d) overall quality of life / patient satisfaction; and e) 'other.' The three most common types of endpoints were: surrogate measures of disease (24/29 trials; 83%); global quality of life / patient satisfaction (15/29 trials; 52%); and resource utilization / cost (14/29 trials; 48%).

Patient outcomes were analysed to determine the impact of NP interventions in 29 RCTs. Almost half of the RCTs (13/29; 45%) described their calculation of the minimum sample size required to ensure a sufficiently high likelihood of yielding statistically significant results;[37] the remaining 16/29 (55%) of the trials did not calculate minimum sample sizes, although 5/29 (17%) of these trials were identified as exploratory pilot studies.[7,45,50,64,65] Nevertheless, the value of statistical significance, reflecting 'technically successful research' that reasonably concludes results are due to the intervention, does not void meaningful test results that are not statistically significant (uncertain relationship between the independent variable of the intervention and the dependent variable of the result), yet may be clinically significant, with results derived from sound scientific study designs.[77] Among the 29 RCTs included in this review, statistically significant differences between NP interventions versus control were observed in a) 16 RCTs relating to surrogate measures of disease;[6,8,44,45,47,50,52-56,60,61,63,66,68] b) 10 RCTs measuring resource utilization / cost;[27,49,50,62,65-67,69,78,79] c) one RCT measuring global / overall quality of life;[52] d) seven RCTs measuring patient satisfaction;[46,48,55,59,60,62,67] and e) four RCTs measuring "other" outcomes[7,62,69,70] [Table 4].

Table 4 Statistically significant NP impact on patient endpoint-outcomes

Physiologic Marker Outcomes	**CVD *** ^^Allen [44] Blood Lipids ^^ Goessens [47] CVD Risk Factors	**Respiratory Disease** ^^ Fairall [8] Tuberculosis Detection (sputum microscopy/ culture)	**Type Two Diabetes Mellitus** ^^ Ralston [6] Glycated Hemoglobin	**Obesity** ^ ter Bogt Risk Factors Associated with Obesity: systolic blood pressure,[56] fasting glucose[80]
i. Symptom Severity **ii. Functional Status** **iii. Behaviour / Lifestyle Change Outcomes**	**CVD *** ^^ Allen [44] iii. Diet and Exercise	**Respiratory Disease** ^^ Berkhof [50] ii. Health Status of Chronic Obstructive Pulmonary Disease **Suspected Ovarian Cancer** ^^ McCorkle [52] i. Cancer-Specific QOL	**Advanced Cancer** ^^ Kim [53] i. Pain Ratings and Cancer-specific QOL **Incontinence** ^^ Williams [60] ^^ Williams, post hoc [81] i. Symptom Severity / Cure	**Obesity** ^ ter Bogt [56] i. Body Weight Loss and Waist Circumference ^ ter Bogt[82] iii. Physical Activity
	Rheumatoid Arthritis ^ Hill [55] i. Fatigue	**Breast Cancer Survivors** ^^ Ganz [61] i. Menopause Symptoms ii. Sexual Functioning	**Addiction** ^^ Mertens [68] iii. Alcohol and Drug Use	**Ischemic Stroke** ^^ Mitchell [54] i. Post-stroke Depression
Drug Utilization Outcomes	**Respiratory Disease** ^^ Fairall [8] Inhaled Corticosteroids	**Emergency Department** ^ McClellan [63] Medication Administration	**CVD** ^^ Ansari [45] Target Use of Beta-Blocker Medication	**Self-Reported Drug Utilization** ^^ Jones [66] Self-reported NSAID Reduction
Acute Resource Utilization / Cost Outcomes	**Emergency Department** ^ Cooper [62] Patient Wait Time			
Outpatient Resource Utilization / Cost Outcomes	**Respiratory Disease** ^ Nathan [49] Clinic Attendance ^^ Berkhof [50] PHC** and Outpatient Clinic Visits	**Suspected Ovarian Cancer** ^^ McCorkle, post hoc [79] Primary Health Care Visits	**Older Adults Post Hospital Discharge** ^^ Enguidanos [65] Physician Office Visits	**Pediatric Eczema** ^ Schuttelaar,post hoc[78] Annual Family Costs per Patient (including Societal Costs)
Primary Health Care Resource Utilization / Cost Outcomes	**Common Complaints** ^ Dierick-van Daele Consult Time and Return Visits[67] Direct Costs per Consult / Study Clinics[27]	**Non-Malignant, Non-Inflammatory Musculoskeletal Pain** ^^ Jones [66] NSAID Costs	**Post-Partum Mother / Infant** ^ Hannan [69] Total Healthcare Charges	
Global Quality of Life Outcomes	**Suspected Ovarian Cancer** ^^ McCorkle[52] SF-12 physical and mental components			
Patient Satisfaction Outcomes	**Minor Injury** ^ Cooper [62]	**Post-Operative to Cardiovascular Surgery** ^^ Tranmer [46] ^^ Sawatsky [48]	**Rheumatoid Arthritis** ^ Hill [55] **Pediatric Eczema** ^ Schuttlelaar [59]	**PHC 'Common Complaints'** ^ Dierick-van Daele [67] **Incontinence** ^^ Williams [60]
Other Outcomes	**Minor Injury** ^ Cooper [62] Quality of Clinical Documentation	**Type One Diabetes Mellitus** ^^ McCarrier [7] Self-Efficacy	**Post-Partum Mother / Infant** ^ Hannan [69] Perceived Maternal Health / Stress	**College Women** ^^ Johnson-Mallard [70] STI Knowledge and Perceived Risk

* Cardiovascular Disease (CVD) ** Primary Health Care (PHC) ^Role Substitution (RS) ^^Interprofessional Team (IPT)

Table 5 Abridged: Results of NP Interventions on primary* patient outcomes, or on the 'first outcome reported' in trials without endpoints pre-specified as primary or secondary (**see Appendix J for complete reporting of patient outcomes in each of 29 RCTs; section 4.6 resumes on page 62)

Author, Year Country **Setting** **Level of Prevention**	**Design, Duration, Study Population** (disease state / health condition / wellness[9])	**Patients (N)**	**NP Intervention Domains (Objective 1)**	**Endpoints (Objective 2)**	**Primary* Patient Outcomes / 'First Outcome Reported' in Studies without pre-specified Primary versus Secondary Endpoints (abridged Objective 3)**
Pioro[71] 2001 U.S. *Acute Care Inpatient* Internal medicine wards at a single center teaching hospital, Cleveland, Ohio, affiliated with Case Western Reserve University **3^0 Tertiary Prevention**[13]	RS^ Admission to 6 weeks post-discharge; 1.5 years study duration 381 patients, 18–69 years, gastro-intestinal, pulmonary, infectious, metabolic/ substance abuse, neurological, cardio-vascular and "other" acute illnesses	*Intervention* = NP-based care (n=193) *Control* = House-staff care (n=188)	Diagnosis Prescribing Clinical Procedures Education	1) *Adverse Events 2**)** *Resource & Cost *Feb. 17, 2017* $1.00 U.S = $1.31 Canadian $0.76 U.S. = $1.00 Canadian 3) **Functional Status 4) **Global Quality of Life	1) *Overall Adverse Events (transfers to ICUs, hospital-acquired complications, and in-hospital mortality) NP 7.5% House-staff 11.8% Difference - 4.3% (95% CI -10.2, 1.6) p > 0.10 2) *Resource & Cost a. Mean length of hospital stay NP 5.0 days House-staff 5.3 days Difference -0.3 (95% CI -1.2, 0.6 days) p > 0.10 b. Mean number of consultations to other services (e.g. respiratory therapy) NP 1.4 House-staff 1.4 Difference -0.0 (95% CI -0.2, 0.3) p > 0.10 c. Mean total hospital charges, costs (U.S.$) NP $8854 House-staff $9426 Difference -$572 (95% CI -$2704, $1560) p > 0.10 d. Mean total ancillary charges, costs (U.S.$) NP $4960 House-staff $5358 Difference -$399 (95% CI -$1820, $1023) p > 0.10

Author, Year Country **Setting** **Level of Prevention**	**Design, Duration, Study Population** (disease state / health condition / wellness[9])	**Patients (N)**	**NP Intervention Domains (Objective 1)**	**Endpoints (Objective 2)**	**Primary* Patient Outcomes / 'First Outcome Reported' in Studies without pre-specified Primary versus Secondary Endpoints (abridged Objective 3)**
Allen[44] 2002 U.S. *Outpatient / Specialized Referral* Outpatient clinic of Johns Hopkins Hospital, Baltimore, Maryland **3[0] Tertiary Prevention**[13] Post hoc analysis: Paez[83] (2006) *Cost-effectiveness* Appendix I-6	IPT ^^ Intervention for one year post-discharge 228 coronary heart disease outpatients who received coronary artery bypass grafting or percutaneous coronary intervention	*Intervention* = NP case management + Enhanced Usual Care (EUC) (n = 115) *Control* = Enhanced Usual Care (EUC) from primary providers &/or cardiologists (n =113)	Diagnosis Prescribing Strategies for Behaviour Change Care coordination	1) *Lipid Goals: Total cholesterol Low density lipoprotein cholesterol (LDL-C, "bad" cholesterol) Triglyceride levels High density lipoprotein cholesterol (HDL-C, "good" cholesterol) 2) **Drug Compliance 3) **Diet and Exercise	1) *Mean (SD) Lipid Levels at 1 year a. Total Cholesterol NP 4.1mmol/L (0.7) EUC 4.6mmol/L (0.6) Difference = 0.5 mmol/L p < 0.0001 b. Low-density lipoprotein cholesterol (LDL-C) NP 2.2mmol/L (0.57) EUC 2.67mmol/L (0.57) Difference = 0.47 mmol/L p < 0.0001 c. Triglycerides NP 3.57 mmol/L (1.53) EUC 4.25 mmol/L (1.79) Difference = 0.68 mmol/L p = 0.002 d. High-density lipoprotein cholesterol (HDL-C) increased modestly in both groups e. Achieved LDL-C treatment goal < 2.59 mmol/L NP 65% EUC 35% Difference = 30% p =0.0001 Hypercholesterolemia defined as LDL-C level > 2.59 mmol/L or total cholesterol level > 5.18 mmol/L

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Jones 2002[66] England *Primary Health Care* Patients were examined at their general practice or their homes, Nottingham-shire **3[0] Tertiary Prevention[13]**	IPT^^ 6 months 222 patients, from 5 general practices, > or = to 18 years; NSAID prescriptions for > or = to 6 weeks of previous year	*'Active Intervention'* = NP assessment, patient-tailored educational package, with request to withdraw NSAIDS and use alternative therapy + Usual GP Care (n =110) *'Control Intervention'* = NP assessment & basic NSAID education + Usual GP Care (n=112)	Diagnosis Prescribing Education *Feb.17, 2017* £ 1.00 Great Britain = $1.62 Canadian £ 0.62 Great Britain = $1.00 Canadian	1) *Self-reported reduction in oral NSAID dose at six months 2) **Changes in total prescription data 3) **NSAID costs; health service costs 4)**Global QOL	1) *Self-reported reduction in oral NSAID dose by 50% or less, at 6 months Active NP Intervention 38 % (42/110) patients Control 13% (14/112) patients Difference = 25% $p < 0.0001$
Ansari[45] 2003 U.S. **Pilot RCT**	IPT ^^ Median follow-up period = 12 months 169 CHF	*Notification Intervention* Internists 10 Cardiologists 2 NPs 3 (n = 64 patients)	Diagnosis Prescribing Education	1) *Target beta blocker use in chronic heart failure patients	1) *Beta Blocker Use a. Patients initiated or up-titrated on beta-blockers Notification group 16% (10/64) NP facilitator 67% (36/54) Control group 27% (14/51) $p < 0.001$

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Outpatient / Specialized Referral Single academic medical centre, San Francisco, California **3[0] Tertiary Prevention**[13]	outpatients randomized into three groups; providers were also individually randomized into three groups, to decrease the likelihood of contamination between patients and providers	*NP Facilitator Intervention* Internists 19 Cardiologists 3 NPs 3 (n = 54 patients) *Control* Internists 16 Cardiologists 4 NPs 4 (n = 51 patients)		2) **Emergency Room visits / Hospitalizations 3) **Mortality	b. Percent patients to target guideline dose Notification group 2% (1/64) NP facilitator 43% (23/54) Control group 10% (5/51) p < 0.001 c. Mean length of time from initiation to target dose (months) Notification 9.3 NP facilitator 5.9 Control 8.5 p < 0.001
Hill[55] 2003 England *Outpatient / Specialized Referral* Traditional rheumatology outpatient clinic managed by Junior	RS ^ Six clinic visits within 12 months study period 80 rheumatoid arthritis (RA) outpatients, 18 years or	*Intervention* = Rheumatology NP (RNP) care (n =39) *Control* = Junior Hospital Doctor (JHD) care (n= 41)	Diagnosis Prescribing Clinical Procedures Strategies for Behaviour Change	1) *Disease Activity Score at 24 and 48 weeks 2) **Plasma Viscosity 3) **Pain physical function psychological status 4) **Changes to medications	1) *Disease Activity Score (DAS28) Week 24 NP 35/39, JHD 34/41 Patients Scores Unchanged: NP 19 JHD 25 Patients Scores Worsened: NP 6 JHD 5 Patients Scores Improved: NP 10 JHD 4 no p-value reported

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Hospital Doctors (JHDs) within a teaching hospital affiliated with the University of Leeds **3^0 Tertiary Prevention**[13]	older, to rheumatology clinic on at least three previous occasions			5) **Lab tests, investigations, referrals 6) **Patient Satisfaction 7) **Knowledge	Week 48 NP 36/39, JHD 35/41 Patients Scores Unchanged: NP 19 JHD 22 Patients Scores Worsened: NP 6 JHD 7 Patients Scores Improved: NP 11 JHD 6 no p-value reported
Tranmer[46] 2004 Canada *Outpatient / Specialized Referral* Patients recruited from teaching hospital affiliated with Queen's University, Kingston, Ontario **3^0 Tertiary Prevention**[13]	IPT ^^ Five week intervention 200 cardiac surgery outpatients, discharged from first cardiac surgery with no stay at Intensive Care Unit	*Intervention* = Usual Care + NP initiated phone contacts (n= 102) *Control* = Usual Care (UC) education booklet, home-care follow-up as necessary, and NP contact information (n= 98)	Diagnosis Education Care Coordination	1) *Global Quality of Life 2) **Post-operative symptom distress 3) **Healthcare Utilization 4) **Patient satisfaction	1) *Mean (SD) Global Quality of Life at 5 weeks post-discharge, SF-36 NP 92/102 UC 92/98 Physical scale NP 36.3 (6.4) UC 36.2 (7.5) Difference 0.04 (95% CI –1.99 to 2.08) p = 0.97 Mental scale NP 50.4 (11.5) UC 51.7 (11.9) Difference –1.25 (95% CI –4.54 to 2.04) p = 0.45

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Fairall[8] 2005 South Africa *Primary Health Care* 40 primary health care clinics in the Free State staffed by NPs; pragmatic cluster RCT with primary health care clinic the unit of random allocation **3^0 Tertiary Prevention**[13]	IPT ^^ Three month study period 1,999 patients with cough or difficult breathing on presentation or within past 6 months	*Intervention* =, an educational outreach program (expanded prescribing provisions with locally tailored guidelines) implemented by NPs 20 clinics; 1000/1999 patients *Control* = Usual Care, no educational outreach 20 clinics; 999/1999 patients	Diagnosis Prescribing Strategies for Behaviour Change	1) *Case detection of tuberculosis by sputum microscopy or culture for tuberculosis 2) *Prescriptions for inhaled corticosteroids to treat asthma; antibiotic prescriptions for upper and lower respiratory tract infections 3) **Number of HIV patients receiving prescriptions for cotrimoxazole prophylaxis	1) *Case detection of tuberculosis (TB) at 3 months Outreach Intervention 6.4% (57/892) Control 3.8% (34/890) OR = 1.72 (95% CI 1.04-2.85) p = 0.04 ICC = 0.007 2) *Prescriptions at 3 months a. Inhaled corticosteroids for asthma Outreach Intervention 13.7% (137/1000) Control 7.7% (77/999) OR = 1.90 (95% CI 1.14 to 3.18) p = 0.006 ICC = 0.019 b. Antibiotics for upper and lower respiratory tract infections Outreach Intervention 39.7% (397/1000) vs Control 39.4% (394/999) OR = 1.01 (95% CI 0.74 to 1.38) p = 0.95 ICC = 0.042

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Goessens[47] 2006 Netherlands *Outpatient / Specialized Referral* Risk-factor management clinic in the University Medical Center, Utrecht 3[0] **Tertiary Prevention**[13] Post hoc analysis Sol[75] (2008) *Self-efficacy* Appendix I-10	IPT ^^ One year intervention 236 cardiovascular disease (CVD) patients with two or more modifiable risk factors: smoking, hypertension dyslipidemia diabetes, obesity, hyperhomocysteinemia	*Intervention* = NP at risk factor management clinic + Usual Care (n=119) *Control* = Usual Care (UC) by GP and treating vascular specialist (n=117) CVDs included: Peripheral arterial disease, Abdominal aortic aneurysm, Cerebrovascular disease, Coronary heart disease	Diagnosis Education At the time of the trial, an NP in the Netherlands was not formally allowed to prescribe; instead, a study physician prescribed or changed medication for patients in the trial	1) *Treatment goals: lipid, blood pressure, BMI (body mass index), blood glucose, homocysteine and smoking 2) **Self-reported drug utilization 3) **Overall quality of life	1)*Percentage of patients who achieved treatment goals at mean follow-up of 14 months (range 10-22) a. Low-density lipoprotein (LDL) cholesterol treatment goal < or equal to 3.1 mmol/L NP 88 UC 67 OR = 3.5 (95% CI 1.5–8.6) b. Total cholesterol (mmol/L) treatment goal < 5.0 mmol/L NP 79 UC 61 OR = 3.3 (95% CI 1.5–7.3) c. Systolic blood pressure (mm Hg) treatment goal < 140 mmHg NP 63 UC 37 OR = 2.7 (95% CI 1.3–5.4) d. Body mass index (kg/m^2) treatment goal < 25 kg/m^2 NP 38 UC 24 OR = 4.0 (95% CI 1.2–13.1) e. Differences non-significant: Diastolic BP, HDL-C, Triglycerides, Fasting Blood Glucose, Homocysteine, Waist Circumference, Smoking

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Nathan[49] 2006 England *Outpatient / Specialized Referral* West Suffolk hospital outpatient clinic **3^0 Tertiary Prevention**[13]	RS ^ 6 month study 154 outpatients > 16 years recently discharged from hospital related to acute asthma	*Intervention* = NP care (n= 78) *Control* = Respirologist care (n=76)	Diagnosis Prescribing Education	1)* Number of acute asthma exacerbations within 6 months of hospital discharge 2) **Peak flow 3) **Disease-specific QOL 4)**Resource utilization	1) *Number acute asthma exacerbations at 6 months NP 98/174 exacerbations Respirologist 76/174 exacerbations Difference 22 exacerbations p = 0.368
McCarrier[7] 2009 U.S. **Pilot RCT** *Outpatient / Specialized Referral* Diabetes Care Center, University of Washington Seattle, Washington **3^0 Tertiary Prevention**[13]	IPT ^^ One year intervention 78 Type I Diabetes outpatients, 21 - 49 years at least one A1c test > or = to 7% in prior year	*Intervention* = NP coordination of Web-based care + usual care (n =42) *Control* = Usual Care (UC) from multidisciplinary practice team at Diabetes Care Center (n = 36)	Diagnosis Education Care Coordination	1) *Difference in mean Hemoglobin A1c from baseline to 12-month follow-up 2) **Diabetes-specific self-efficacy	1) *Mean (SD) change hemoglobin A1c values at 1 year NP - 0.37 (1.3) UC: + 0.11 (1.4) Absolute difference = 0.48 (95% CI -1.2 2 to 0.27) p = 0.160

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Mitchell[54] 2009 U.S. *Outpatient / Specialized Referral* Outpatient clinic, including rehabilitation facilities, University of Washington Seattle, Washington **3[0] Tertiary Prevention**[13]	IPT ^^ 8 week intervention within 24 months 101 patients within 4 months of an ischemic stroke and diagnosis of clinical depression; follow-up contact included patients' private homes	*Intervention* = Psychosocial intervention (9 NP sessions) + Usual Care, including antidepressants (n=48) *Control* = Usual stroke provider care (UC), including antidepressants (n=53)	Diagnosis Strategies for Behaviour Change	1) *Post-stroke depressive symptomology (reduction in depressive symptoms) 2) **Limitations in ability (physical function), participation and overall stroke impact	1) *Mean change (SD) Hamilton Rating Scale for Depression (HRSD), 12 months NP - 9.2 (5.7) 44/48 patients UC - 6.2 (6.4) 48/53 patients Difference -2.9 (CI -5.4 to -0.4) p=0.023 • Remission (defined as HRSD < or = 9) at 9weeks NP 47% (45/48) UC 19% (53/53) Difference 28 % OR = 4.8 (CI 1.8 to 12.9) p = 0.001 • Remission at 21weeks NP 46% (46/48) UC 22% (50/53) Difference 24% OR=3.4 (CI 1.3 to 8.7) p = 0.008 • Remission at 12 months NP 48% (44/48) UC 27% (48/53) Difference21% OR=2.7 (CI 1.1 to 6.6) p = 0.031 • Remission at 24 months NP 65% (44/48) UC 46% (48/53) Difference 19% OR =2.3 (CI 0.8 to 6.7) p = 0.130

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Ralston[6] 2009 U.S. *Outpatient / Specialized Referral* University of Washington Internal Medicine Clinic **3[0] Tertiary Prevention**[13]	IPT ^^ 12 months 83 Type II Diabetes outpatients, 18-75 years, glycosylated hemoglobin > or = to 7% at least 2 clinic visits in prior year	*Intervention* = NP coordination of Web-based care + Usual Care (n=42) *Control* = Usual Care (UC) from an internal medicine physician (n=41)	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	1) *Absolute change in glycated hemoglobin at 12 months 2) **Blood pressure, total plasma cholesterol 3) **Healthcare utilization	1) *Absolute change in glycated hemoglobin at 12 months Target for glycated hemoglobin is < 7% A1c, equivalent to blood glucose concentration < than 8.6 mmol/L NP 33% at target UC 11% at target Difference 22% p = 0.03
Huizinga[51] 2010 U.S. *Outpatient / Specialized Referral* Outpatient clinic of Johns Hopkins Hospital, Baltimore, Maryland **3[0] Tertiary Prevention**[13]	IPT ^^ Two year study 165 Type II Diabetes outpatients, 18-75 years, with recent glycemic control	*2 Intervention Groups* 'Usual Care + NP phone contact' 1) Quarterly contact, every 3 months (n =55) 2) Monthly contact (n =55) *Control* = Usual Care in Diabetes Improvement Program (n= 55)	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	1)*Glycemic relapse	1)*Glycemic relapse, defined as an increase in HbA1c of > or = to 1% over baseline, at 2 years • Quarterly contact 21% (10/48) patients relapsed • Monthly contact 29% (15/52) patients relapsed • Usual care 25% (12/48) patients relapsed p = 0.83 Prevalence of relapse did not differ between groups over follow-up time, nor did the cumulative incidence of relapse differ between treatment groups (p = 0.72)

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Kim[53] 2013 South Korea *Outpatient / Specialized Referral* Pain Clinic of the Yonsei University Health System**,** Seoul **3[0] Tertiary Prevention**[13]	IPT ^^ 1 week intervention 108 advanced cancer outpatients, 20 - 80 years moderate level of cancer-related pain	*Intervention* = Usual Care + daily phone monitoring (tele-monitoring) by NP (n = 54) *Control* = Usual Care (UC) with standardized pain education by NP (n = 54)	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	1) *Reduction in average pain levels 2) **Performance status / functional impairment; anxiety/ depression, distress 3) **Cancer specific symptoms (EORTC QLQ-C30)	1)*Reduction in average pain ratings on Brief Pain Inventory in Intervention group compared to control, at 1 week (0 = no pain; > or = to 4 = average pain; 10 = 'pain as bad as you can imagine') Number patients experiencing average pain intensity at 1 week NP 19% (10/54) UC 35% (19/54) Difference 16% p = 0.02
Sawatsky[48] 2013 Canada O*utpatient / Specialized Referral* St. Boniface Hospital, University of Manitoba, Winnipeg, Manitoba **3[0] Tertiary Prevention**[13]	IPT ^^ Six week intervention 204 cardiac surgery outpatients following first time coronary artery bypass graft	*Intervention* = Usual Care + NP phone contact (n= 97) *Control* = Usual Care (UC) primary care appointment within 1 week, visit to cardiac surgeon for all patients at 6 weeks (n=107)	<u>All 5 domains</u>: Diagnosis Prescribing Clinical Procedures Education Care Coordination	1) *Global quality of life 2) **Symptoms in cardiac surgery recovery 3) **Health resource use 4) **Patient satisfaction	1)* Mean (SD) Global Quality of Life at 2 and 6 weeks post-discharge, SF-36 Physical component 2 weeks NP 19.0 (3.4) UC 18.0 (3.4) p = 0.04 6 weeks NP 22.2 (4.2) UC 22.0 (4.0) p = 0.69 Mental component 2 weeks NP 21.5 (2.1) UC 21.5 (2.3) p = 0.87 6 weeks NP 21.3 (2.3) UC 21.1 (2.3) p = 0.67

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Berkhof[50] 2014 Netherlands **Pilot RCT** *Outpatient / Specialized Referral* Large teaching hospital in Zwolle, Netherlands **3[0] Tertiary Prevention**[13]	IPT ^^ 2 year study 100 COPD (Chronic Obstructive Pulmonary Disease) outpatients > or = to 40 years, COPD GOLD (Global initiative for staging Obst ructive Lung Disease: 1 = mild; 4 = very severe), stage > or = to 2, smoking history > 10 pack-years	*Intervention* = patient-initiated visits with pulmonary NP upon increase of symptoms. NP followed an 'on-demand protocol' with consult to pulmonologist for urgent problems (n =49) *Control* = Usual Care (UC) via outpatient visits initiated by pulmonologist, to either the pulmonologist or to the pulmonary NP (n=51)	Diagnosis Prescribing Education *Feb. 17, 2017* €1.00 Euro = $1.53 Canadian €0.72 Euro = $1.00 Canadian	1) *Mean change in Clinical COPD Questionnaire (CCQ) 2) **Time to first exacerbation COPD 3) **Visits to general practice physicians, pulmonologists, and pulmonary NPs 4) **Total treatment costs 5) **Disease-specific quality of life (St. George's Respiratory Questionnaire, SGRQ) 6) **Global quality of life	1) *****Mean (SE) change COPD status at 2 years Lower score on Clinical COPD Questionnaire (CCQ) = less deterioration / better health status Minimal clinically important difference (MCID) of CCQ total score is 0.4 Symptom domain of the CCQ NP 0.14 (+ or - 0.14) in 40/49 patients UC 0.58 (+ or - 0.16) in 29/51 patients Difference = - 0.44 (+ or - 0.21) 95% CI -0.87 to -0.023 p = 0.04 Absolute difference between groups of 0.44 met the MCID for a clinically relevant effect

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Mertens[68] 2014 South Africa *Primary Health Care* Large public sector primary healthcare clinic in Delft, near Cape Town **3^0 Tertiary Prevention**[13]	IPT ^^ Three month study period 403 patients 18–24 years of low socio-economic status, screened for high-risk alcohol and / or drug use	*Intervention* = session of Brief Motivational Interviewing (average session 10 minutes) by NP + referral list of resources (n=206) *Control* = minimally enhanced usual care with referral list of resources (n=197)	Strategies for Behaviour Change	1)*Rates of at-risk alcohol use and drug use at three month follow-up	1) *****Mean percent reduction in ASSIST scores at 3 months (Alcohol, Smoking and Substance Involvement Screening Test) • Alcohol NP 38.3 % Control 20.9% p = 0.0293 • Cannabis NP 28.3% Control 9.8% p = 0.1119 • Methamphetamine NP 57.2% Control 76.9% p = 0.2264
Ganz[61] 2000 U.S. *Outpatient / Specialized Referral* Jonsson Comprehensive Cancer Center, University of California,	IPT ^^ Intervention period of 4 months 76 surviving breast cancer patients with abruptly recurred menopausal	*Intervention* = comprehensive menopausal assessment (CMA) delivered by NP (n=37) *Control* = Usual Care (UC) + 1 contact from	Diagnosis Prescribing Strategies for Behaviour Change	1) *Composite menopausal symptom scale 2) **Vitality, from Medical Outcomes Study Short Form 36 (SF-36)	1) *Menopause symptom-scale score, mean change (reduction) from baseline to 4 months NP 0.61 (95% CI 0.40–0.82) 33/37 patients UC 0.19 (95% CI −0.06 to 0.44) 39/39 patients p = 0.0004

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Los Angeles, California **2^0 Secondary Prevention**[13]	symptoms, due to discontinued estrogen replacement therapy related to breast cancer	research assistant at 2 months, asking of therapies for symptom management (n= 39)		3) **Cancer Rehabilitation Evaluation System (CARES) Sexual Functioning Scale	
Cooper[62] **2002** Scotland *Acute Care Emergency Department* A single Accident and Emergency Department of Glasgow Royal Infirmary, Glasgow **2^0 Secondary Prevention**[13]	RS ^ 2 month study duration 204 patients over 16 years, with minor injury that fell within the emergency NP (ENP) protocol	*Intervention* = ENP care (n = 102) *Control* = Senior House Officer (SHO) care (n = 102)	Diagnosis Prescribing Clinical Procedures Education	1) Resource Utilization: consult time and referral to follow-up clinics 2) Unplanned Follow-up 3) Missed Injuries 4) Patient Satisfaction 5) Quality of Clinical Documentation 6) Recovery at one month	*Endpoints not pre-specified as primary / secondary* 1st Outcome Reported 1) Resource Utilization a. Patient's average wait time: ENP 48.6 minutes SHO 70.1 minutes 95% CI 11.2–31.8 minutes, $p < 0.001$ b. Total consult time (including treatment time): ENP 30.0 minutes SHO 24.9 minutes 95% CI -1.3 to 11.5 minutes, $p < 0.115$ c. Seeking advice from senior medical staff [when X-ray interpretation for which ENPs were required to consult was excluded; SHOs were not required to consult X-ray interpretation] ENP 20.9% SHO 11.5%, $p < 0.21$ d. Numbers of X-rays requested ENP 56.6% SHO 47.5%, $p = 0.2$ e. Referral to follow-up clinics ENP 33.3 % SHO 27.5%, $p = 0.358$

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Williams [60] 2005 England *Primary Health Care* Patients' homes in Leicestershire Rutland **2^0 Secondary Prevention**[13] Post hoc analysis Williams[81] (2011) *Long term follow-up* Appendices I-3, I-**7**	IPT ^^ Six month intervention 3746 patients aged 40 years and over living in private households; incontinence several times per month or more to several times a year; reported impact of symptoms on quality of life	*Intervention* = continence service provided by NPs (n = 2958) *Control* = usual primary care, GP and continence advisory services (n=788) 4:1 ratio was deemed necessary to ensure sufficient intervention data for evaluation of detrusor over-activity and urodynamic stress incontinence	Diagnosis Prescribing Education *Feb.17, 2017* £ 1.00 Great Britain = $1.62 Canadian £ 0.62 Great Britain = $1.00 Canadian	1) *Improvement in one or more symptoms of which cure (no symptoms) is a subset 2) **Number of symptoms alleviated 3) **Resources: healthcare professional contacts, investigations; cost-effectiveness 4) **Patient satisfaction and patient perception of problem	1) *Improvement in 1 or more symptoms incontinence, urgency, frequency, nocturia a. 3 months NP 60% (1417/ 2378 responders) Control 48% (281/584 responders) Difference 12% (95% CI 7 to 16%) p < 0.001 b. 6 months NP 62% (1369/2201 responders) Control 52% (277/536 responders) Difference 10% (95% CI 6 to 15%) p < 0.001 Cure = 0 symptoms a. 3 months NP 25%, 591/2378 Control 15%, 88/584 Difference 10% (95% CI 6 to 13%) p < 0.001 b. 6 months NP 28%, 624/ 2201 Control 19%, 104/536 Difference 9% (95% CI 5 to 13%) p < 0.001

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Krichbaum[64] 2007 U.S **Pilot RCT** *Outpatient / Specialized Referral* Follow-up at subacute, long term care, rehabilitation facilities, and private homes **2^0 Secondary Prevention[13]**	IPT ^^ Six month intervention in 12 month study 33 hip fracture surgery outpatients > or = 65 years, recruited from two hospitals in St. Paul, Minnesota	*Intervention* = usual care + post-acute care coordination by mobile gerontologic NP (n=17) *Control* = usual care by hospital and individual surgeon's protocols (n=16)	Diagnosis, Prescribing (medication reconciliation) Strategies for Behaviour Change	1) Self-rated health 2) Level of geriatric depression 3) Activities of daily living (ADLs) and instrumental activities of daily living (IADLs)	*Endpoints not pre-specified as primary / secondary* 1st Outcome Reported 1) Self-rated health (Global Health (GH) self-ratings - higher scores better) Mean (SD) symptoms at 12 months NP 4.1 (0.95) Control 4.0 (0.71) Difference non-significant

Author, Year Country **Setting** **Level of Prevention**	**Design, Duration, Study Population** (disease state / health condition / wellness[9])	**Patients (N)**	**NP Intervention Domains (Objective 1)**	**Endpoints (Objective 2)**	**Primary* Patient Outcomes / 'First Outcome Reported' in Studies without pre-specified Primary versus Secondary Endpoints (abridged Objective 3)**
Dierick-van Daele[67] 2009 Netherlands *Primary Health Care* Trial affiliation University of Maastricht; Foundation for Development of Quality Care in General Practice, Eindhoven **2^0 Secondary Prevention**[13] Post hoc analysis Dierick-van Daele[27] *Economic evaluation* Appendix I-7	RS ^ Two week intervention in six month study 1,591 from 15 general practices, patients 16 years and older, with respiratory/ throat, ear/nose musculoskeletal/skin injuries, urinary/ gynaecological / geriatric problems	*Intervention* = patient care from newly graduated NP (Master Degree of Advanced Nursing Practice), experience ranging from 1 to 5 years; 12 NPs (n = 817) *Control* = patient care from GP with an average of 16 years' experience; 50 GPs (n = 684)	Diagnosis Prescribing Education	1) Duration of consultation 2) Medical resource use 3) Number of prescriptions given 4) Patient satisfaction and patient perceptions of quality of care	*Endpoints not pre-specified as primary / secondary* 1st Outcome Reported 1) Duration of consultation (minutes), mean (SD) NP 12.22 (5.7 minutes) GP 9.20 (4.8 minutes) $p < 0.001$

Author, Year Country **Setting** **Level of Prevention**	**Design, Duration, Study Population** (disease state / health condition / wellness[9])	**Patients (N)**	**NP Intervention Domains (Objective 1)**	**Endpoints (Objective 2)**	**Primary* Patient Outcomes / 'First Outcome Reported' in Studies without pre-specified Primary versus Secondary Endpoints (abridged Objective 3)**
McCorkle[52] 2009 U.S. *Outpatient / Specialized Referral* Patient contact made at private homes or by phone, northeast Connecticut Trial approved by Yale University, New Haven, Connecticut **2^0 Secondary Prevention**[13] classification with regards to *suspected* (not definitive) ovarian cancer, the study's target disease	IPT ^^ Six month study 149 post-surgical outpatients 21 years or older, with suspected primary diagnosis of ovarian cancer after abdominal surgery, prognosis of at least 6 months, with order to initiate chemo-therapy	*Intervention* = 18 contacts by an oncology NP, supported by psychiatric NP (PSYNP) consults (32/74 intervention patients) when warranted for high emotional distress = Distress Thermometer > or = to 4 (n=74) *Attention Control* = nine contacts by research assistant, supported by medical social worker (no data for patient contact with social worker) (n = 75)	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	*Quality of Life (QOL) <u>1. Cancer specific</u> a) Center for Epidemiological Studies - Depression (CES-D) b) Ambiguity subscale of the Mishel 'Uncertainty in Illness' Scale (MUIS) c) Symptom Distress Scale (SDS) <u>2. Overall / Global QOL</u> a) SF-12 physical component b) SF-12 mental component	*QOL was measured at baseline (24–48 hours after surgery), 1, 3, and 6 months post-surgery **3 types of mixed effect regression models** estimated the 'rates of change' (effect estimates) in different QOL measures over time: **(1)** Oncology NP intervention without PSYNP (Appendix J) **(2)** Oncology NP intervention with PSYNP • Rate of reduction in MUIS score & Rate of improvement in the SF-12 score was significantly greater for intervention vs control: <u>Uncertainty of Illness (MUIS)</u> effect estimate = - 0.03917 ± se 0.00915, $p < 0.0001$ <u>SF-12 mental component</u> effect estimate = 0.02300 ± se 0.00748, $p = 0.0023$ • Rate of change in CES-D scores was significantly greater for control vs intervention <u>CES-Depression (CES-D)</u> effect estimate = 0.03594 ± se 0.01213, $p = 0.0033$ • Poor model fit - no effect estimate data for SDS or SF-12 physical <u>Symptom Distress Scale (SDS)</u> <u>SF-12 physical component</u> **(3)** PSYNP separate from Oncology NP (Appendix J) Post hoc analysis: McCorkle[79] (2011) *Healthcare utilization* Appendix I-6

Author, Year Country **Setting** **Level of Prevention**	**Design, Duration, Study Population** (disease state / health condition / wellness[9])	**Patients (N)**	**NP Intervention Domains (Objective 1)**	**Endpoints (Objective 2)**	**Primary* Patient Outcomes / 'First Outcome Reported' in Studies without pre-specified Primary versus Secondary Endpoints (abridged Objective 3)**
ter Bogt[56] 2009 Netherlands *Primary Health Care* 11 general practices (1-7 GPs and 1-3 NPs per location), Groningen, northern Netherlands **2[0] Secondary Prevention**[13] although now considered a chronic disease, obesity is reversible, thus secondary prevention	RS ^ One year study 457 patients with BMI 25 – 40 kg/m^2 and either hypertension dyslipidemia or both Obese: BMI > or = to 30 kg/m^2 Overweight: BMI < 30kg/m^2	*Intervention* = low-intensity (for prevention of additional weight gain) lifestyle counseling by NPs (n =225) *Control* = usual primary health care from GPs (n = 232)	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	1) *Changes in body weight after one year of intervention 2) **Waist circumference 3) **Blood pressure, total cholesterol, and fasting glucose one year after intervention	1) *****Percentage change in body weight at 1 year NP -1.9% (95% CI -2.5, -1.2) 200/225 patients UC -0.9% (95% CI -1.5, -0.2) 214/232 patients Difference 1.0% $p < 0.05$ Weight losers (successful) and stabilizers (percentage of subjects who gained less than 1% body weight by end of study) at 1 year Women NP 72.8% (75/103) patients UC 64.0% (73/114) patients Difference 8.8% non-significant Men NP 80.6% (79/98) patients UC 65.3% (66/101) patients Difference 15.3% $p < 0.05$ Post hoc analysis ter Bogt[82] (2011) *One-Year Follow-up* Appendix I-3 Post hoc analysis ter Bogt[80] (2011) *Three-Year Follow-up* Appendices I-2, I-3 Post hoc analysis Driehuis[84] (2012) *Three-Year Follow-up* Appendix I-3

Author, Year Country **Setting** **Level of Prevention**	**Design, Duration, Study Population** (disease state / health condition / wellness[9])	**Patients (N)**	**NP Intervention Domains (Objective 1)**	**Endpoints (Objective 2)**	**Primary* Patient Outcomes / 'First Outcome Reported' in Studies without pre-specified Primary versus Secondary Endpoints (abridged Objective 3)**
Schuttelaar[59] 2010 Netherlands *Outpatient / Specialized Referral* Dermatology outpatient clinic at the University Medical Center, Groningen **2^0 Secondary Prevention**[13] Post hoc analysis: Schuttelaar[78] *Costs and cost-effectiveness analysis* Appendix I-6	RS ^ 1 year study 160 patients < 16 years: 80 patients aged < or = to 4 years & 80 patients aged 4–16 years, all new referrals from GPs or pediatricians with a diagnosis of eczema	*Intervention* = NP-led care (n = 81): Age < or = to 4 years (n = 40) Age 4-16 years (n = 41) *Control* = conventional care by dermatologist (n = 79) Age < or = to 4 years (n = 40) Age 4-16 years (n = 39)	Diagnosis Prescribing Strategies for Behaviour Change	1) *Change in quality of life of the child at 12 months 2) **Eczema severity 3) **Family impact of childhood eczema 4) **Patient satisfaction at 4, 8, and 12 months	1) *Eczema-specific Quality of Life (higher scores representing a poor quality of life) at 12 months • Infants' Dermatitis Quality of Life Index, mean (SD) NP 5.7 (5.4) Dermatologist 5.6 (3.9) p = 0.26 • Children's Dermatology Life Quality Index, mean (SD) NP 4.9 (3.5) Dermatologist 5.6 (4.2) p = 0.55

Author, Year Country **Setting** **Level of Prevention**	**Design, Duration, Study Population** (disease state / health condition / wellness[9])	**Patients (N)**	**NP Intervention Domains (Objective 1)**	**Endpoints (Objective 2)**	**Primary* Patient Outcomes / 'First Outcome Reported' in Studies without pre-specified Primary versus Secondary Endpoints (abridged Objective 3)**
Enguidanos[65] 2012 U.S **Pilot RCT** *Outpatient / Specialized Referral* Health Maintenance Organization (HMO), Los Angeles County, California **2^0 Secondary Prevention**[13]	IPT ^^ 6 months 199 at-risk hospitalized older adults discharged home without in-home care (e.g., home health/ hospice) or caregivers	*Intervention* = Brief NP Transition: up to 3 home visits, 2 phone calls within 72 hours of discharge (n = 100) *Control* = usual care, case management services (wait time 2-14 days) (n =99)	Diagnosis Prescribing (medication reconciliation) Education Care Coordination	1) Efficacy in Self-Care 2) Home Care Patient Satisfaction 3) Emergency room visits, hospital re-admission, days re-hospitalized, physician office visits, and home health care days	*Endpoints not pre-specified as primary / secondary* 1st Outcome Reported 1) Efficacy in Self-Care at 6 months No significant differences between groups
McClellan[63] 2012 England *Acute Care Emergency Department* A single, inner city, adult ED of University Hospitals Bristol	RS ^ Eight week study period 372 patients with peripheral soft tissue injury, older than 16 years	*Intervention* = patient management arrival to discharge by Emergency NP or Extended Scope Physio-therapist (ESP) ENP (n = 123) ESP (n = 126)	Diagnosis Prescribing Clinical Procedures Education	1) *Functional recovery to upper / lower extremity 2) **Preference-based health utility scores 3) **Medication administration 4) **Global quality of life	1) *Functional recovery to upper / lower extremity at 8 weeks Percentage return to normal function, MCID of 9 95% Confidence Intervals Dr 45 to 80 (63.3%) (68/123) ESP 52.5 to 65.0 (59.2%) (72/126) ENP 55.0 to 66.3 (60.0%) (73/123) Equivalence Trial - designed to show that two interventions do not differ by more than a pre-specified unimportant margin;[85] equivalence margin was set at five (calculated using the smallest minimal clinically important difference (MCID) from all outcome measures)

Author, Year Country **Setting** **Level of Prevention**	**Design, Duration, Study Population** (disease state / health condition / wellness[9])	**Patients (N)**	**NP Intervention Domains (Objective 1)**	**Endpoints (Objective 2)**	**Primary* Patient Outcomes / 'First Outcome Reported' in Studies without pre-specified Primary versus Secondary Endpoints (abridged Objective 3)**
2[0] Secondary Prevention[13]		*Control* = routine doctor care from arrival to discharge (n =123)		5) **Number of days unable to work	Post hoc analysis McClellan[86] (2013) *A randomised trial comparing the cost effectiveness of different emergency department healthcare professionals in soft tissue injury management* Appendix I-5
Johnson-Mallard[70] 2007 U.S. *Primary Health Care* Set at two different universities; study authors affiliated with the University of South Florida, Tampa, Florida **1[0] Primary Prevention**[13]	IPT ^^ 2 week study 104 female college students, 18-48 years, in presumably good health, not exposed to lectures on sexually transmitted infections	*Intervention* = a brief, 30 minute educational / behavioral intervention delivered by an NP at one week (n =51) *Control* = no educational / behavioral intervention (n = 53)	Education	1) Knowledge of sexually transmitted infections (STIs) including knowledge of pre and post-natal morbidity / mortality 2) Perceived risk of sexually transmitted infection	*Endpoints not pre-specified as primary / secondary* 1st Outcome Reported 1) STI knowledge survey two weeks following the initial pre-test (higher scores indicate greater knowledge of STIs), one week post intervention, mean (SD) NP Education 26.1 (2.6) Control 21.0 (2.3) $p < 0.0001$

Author, Year Country Setting Level of Prevention	Design, Duration, Study Population (disease state / health condition / wellness[9])	Patients (N)	NP Intervention Domains (Objective 1)	Endpoints (Objective 2)	Primary* Patient Outcomes / 'First Outcome Reported' in Studies without pre-specified Primary versus Secondary Endpoints (abridged Objective 3)
Hannan[69] 2012 U.S. *Primary Health Care* Study patients were recruited prior to discharge from Jackson Memorial Hospital, in the inner city of Miami, South Florida **1^0 Primary Prevention**[13]	RS ^ 1st 2 months post-birth 139 healthy first-time mothers, 18 years or older, each of whom delivered a healthy, full-term single infant; low-income family	*Intervention* = follow-up phone-calls by pediatric NP with 'back-up' pediatric physician available for consultation (n =70) *Control* = routine pediatrician appointment in 2 months (n =69)	Diagnosis Education Care Coordination *Feb. 17, 2017* $1.00 U.S = $1.31 Canadian $0.76 U.S. = $1.00 Canadian	1) Maternal health 2) Infant health 3) Infant morbidity: urgent care visits, Emergency Room (ER) visits, hospitalizations 4) Health care charges: urgent care visits, Emergency Room (ER) visits, and re-hospitalizations	*Endpoints not pre-specified as primary / secondary* 1st Outcome Reported 1) Maternal Health Outcomes at 2 months Post Birth • Mean (SD) Perceived Maternal Health NP 18.61 (1.74) Control 17.2 (2.69) $p < 0.0004$ • Mean (SD) Perceived Stress NP 14.71(3.95) Control 24.64(4.61) $p < 0.0001$ • Perception of Social Support Differences non-significant

*Primary Endpoint **Secondary Endpoint ^Role Substitution (RS) ^^Interprofessional Team (IPT)

17 Tertiary (3^0) Prevention[13] **RCTs** Pioro (2001),[71] Allen (2002),[44] Jones (2002),[66] Ansari (2003),[45] Hill (2003),[55] Tranmer (2004),[46] Fairall (2005),[8] Goessens (2006),[47] Nathan (2006),[49] McCarrier (2009),[7] Mitchell (2009),[54] Ralston (2009),[6] Huizinga (2010),[51] Kim (2013),[53] Sawatsky (2013),[48] Berkhoff (2014),[50] Mertens (2014)[68]

10 Secondary (2^0) Prevention[13] **RCTs** Ganz (2000),[61] Cooper (2002),[62] Williams (2005),[60] Krichbaum (2007),[64] Dierick-van Daele (2009),[67] ter Bogt (2009),[56] Schuttelaar (2010),[59] McCorkle (2009),[52] Enguidanos (2012),[65] McClellan (2012)[63]

2 Primary (1^0) Prevention[13] **RCTs** Johnson-Mallard (2007),[70] Hannan (2012)[69]

**see Appendix J for complete reporting of patient outcomes in each of 29 trials

4.6.1 Clinical Endpoint-Outcomes (life threatening events or death)

Only three trials out of the 29 RCTs identified in this review measured clinical outcomes,[45,49,71] with no statistically significant differences detected[87,88] [Appendix I-1]. However, two of these interventions were tested in a RS design where the NP was compared to another practitioner.[49,71] The third trial was a pilot IPT study that was significantly underpowered for comparison between three groups, with clinical endpoints measured as secondary endpoints (the primary endpoint was drug utilization).[45] Further, pilot studies are usually underpowered as they are not formally powered to assess effect;[89] their main focus is one of feasibility rather than statistical significance,[90] with recommendations to not provide formal significance levels for pilot studies.[89]

The RS trial that evaluated care provided by NPs and usual house staff to hospitalized patients in internal medicine wards, detected no statistically significant differences in clinical outcomes.[88] The percentage of patients experiencing a composite outcome of transfers to intensive care units (ICUs), hospital acquired complications, and in-hospital mortality was 7.5% among NP treated patients compared to 11.8% in the house staff group ($p > 0.1$).[71] However, a serious breach following the randomization process may have resulted in a NP intervention group with less severe disease than controls. Crossover of 89/193 (46%) patients to the house-staff ward occurred after randomization for the following reasons: 1) unavailability of beds on the NP ward, accounting for approximately a third of the crossovers; 2) request of attending doctors wanting the flexibility to pre-empt randomization according to patient health status, accounting for approximately 20% of the crossovers; and 3) NPs' concerns that staffing was inadequate to accept new admissions, particularly for patients requiring frequent 'off-hours' monitoring, with NPs only scheduled to be at the hospital between 0730-2000 hours on weekdays, and for morning rounds on weekends[71] [Table 5, Appendices G and I-1].

The second RS trial measured the clinical endpoint 'number of acute exacerbations at six months' as its primary endpoint, and detected no statistically significant differences between asthma patients receiving care from a NP versus a respirologist.[49] A total of 174 acute exacerbations were recorded over the six-month study period, with 98/174 (56%) occurring in the NP group and 76/174 (44%) occurring the respirologist group, $p = 0.368$. Four types of acute exacerbations were further analysed according to: 1) hospital readmission; 2) emergency nebulization; 3) number of exacerbations requiring any emergency treatment; and 4) the number of exacerbations requiring an additional intervention of intravenous or oral steroids during exacerbation. However, differences between groups in

all four types of acute exacerbations were also not statistically significant[49] [Table 5 and Appendix I-1].

Only one IPT trial that was a pilot study, evaluated the impact of a NP intervention on clinical outcomes.[45] Clinical endpoints of emergency room (ER) visits, hospitalizations and mortality were secondary measures [Appendix J], with data collected as an indicator of safety (to confirm no increase in adverse events), not efficacy (reduction in adverse events).[45] Seventy four providers were randomized into three groups, with each group comprised of internists, cardiologists, and NPs. One group provided usual care, another provided care enhanced with notifications for drug treatment, and the third group utilized NPs to facilitate the initiation, titration and stabilization of patients on beta blocker medication. At 12 month follow-up, no statistically significant differences were observed in the percentage of patients requiring ER care or hospitalization: usual care group 49% (25/51), notification group 45% (29/64), and NP facilitator group 43% (23/54), p = 0.81. Although all-cause mortality was measured, the results could not be interpreted due to a lack of power (i.e. only one death was recorded in the notification group) [45] [Appendices I-1 and J]. Measurements of hospitalization in all other studies of this review focussed on all-cause hospitalizations in the context of health care utilization, and thus were reported under the category of 'resource utilization / cost.'

4.6.2 Surrogate Measures of Disease Endpoint-Outcomes (physiologic markers, 'symptom severity, functional status, behaviour / lifestyle change,' and drug utilization)

Surrogate measures of disease control were assessed in the majority of this review's trials (24/29; 83%). Among these, 'symptom severity, functional status, behaviour / lifestyle change' endpoints were the most commonly evaluated, in 18/29 trials [Appendix I-3]. Drug utilization endpoints were measured in eight of this review's 29 trials [Appendix I-4], while physiologic markers were measured in eight of the trials measuring chronic disease [Appendix I-2].

Physiologic Surrogate Markers

In the eight RCTs containing physiologic surrogate markers as endpoints, cardiovascular risk factors (e.g. blood pressure, blood lipids including cholesterol) and blood glucose indices were the most common markers tested. However, other markers such as lung sputum tests for tuberculosis, and plasma viscosity related to inflammation in rheumatoid arthritis, were also observed in this review. Five study interventions were associated with statistically significant improvements; four used an IPT design and one used a RS design.

The largest impact on physiologic markers was observed in a study where NPs diagnosed status of hypercholesterolemia in post-operative coronary heart disease (CHD) patients.[44] Activities of the NP intervention in this study included medication adjustment according to a study algorithm, and lifestyle counselling for behaviour change strategies with follow-up phone contact. Sixty-five percent of patients in the NP group compared to 35% of patients in the usual care group achieved the American National goal for low density lipoprotein cholesterol in CHD patients ($p = 0.0001$) [44] [Table 5; Appendix I-2]. A similar study of vascular disease patients reported statistically significant improvements in achievement of treatment goals related to multiple types of physiologic markers: systolic blood pressure (OR = 2.7; 95% CI 1.3–5.4), total cholesterol (OR = 3.3; 95% CI 1.5–7.3), low density lipoprotein (LDL) cholesterol (OR = 3.5; 95% CI 1.5–8.6), and body mass index (OR = 4.0; 95% CI 1.2–13.1).[47] However, between-group differences for diastolic blood pressure, high density lipoprotein (HDL) cholesterol, triglycerides, fasting blood glucose, homocysteine levels, waist circumference, and smoking were not statistically significant[47] [Table 5; Appendix I-2].

Virtually the same set of cardiovascular risk factors were measured in a study examining the effect of a behaviour change intervention delivered by NPs to obese patients,[56] with secondary endpoints [Appendix J] including total cholesterol and components of metabolic syndrome: a combination of at least three risk factors (including high fasting blood glucose, high blood pressure, low level of high-density lipoprotein cholesterol, high level of triglycerides, and abdominal obesity) being associated with an increased risk for development of diabetes and cardiovascular disease.[3] While no significant differences were observed with respect to total cholesterol or fasting glucose concentrations between groups, analysis of groups stratified by gender revealed a greater reduction in systolic blood pressure of 14 mmHg for obese men in the NP group compared to a reduction of 5 mmHg in obese men from the usual care group ($p < 0.05$)[56] [Appendices I-2 and J]. In one of three post-hoc analyses, physiologic markers of blood pressure, fasting glucose, and blood lipids were again measured after three years, where a statistically significant improvement in fasting blood glucose was reported, with a reduction in the NP group of - 0.02 mmol/L versus an increase in the GP group of 0.10 mmol/L ($p = 0.02$). Between-group differences in patient outcomes of total cholesterol and systolic blood pressure were non-significant[80] [Appendix I-2]. Blood glucose was also favourably impacted by a NP intervention targeting patients with type two diabetes, using a web-based platform. Target levels of glycosylated hemoglobin (A1c < 7%)

were achieved in 33% of participants in the NP group compared to 11% in usual care after 12 months (p =0.03)[6] [Table 5; Appendix I-2].

No significant differences were detected in two RCTs measuring endpoints of glycemic control, related to both type one[7] and type two[51] diabetes. A web-based NP intervention for patients with type one diabetes and moderate-to-poor glycemic control at baseline, did not find statistically significant reductions in hemoglobin A1c values, despite non-significant improvements at each time point examined.[7] A trial testing a NP phone intervention for patients who had recently achieved glycemic control in their type two diabetes, found no statistically significant differences between groups in the outcome of reduced glycemic relapse[51][Table 5; Appendix I-2].

Physiologic markers were also used to evaluate NP interventions among patients with other medical conditions. Educational outreach and NP management of respiratory diseases in patients from 20 primary care clinics located within an impoverished area of South Africa, was associated with improved detection of tuberculosis (OR 1.72, 95% CI 1.04 to 2.85, p = 0.04, ICC = 0.007) [8] [Table 5; Appendix I-2]. At an outpatient specialist clinic for rheumatoid arthritis, physiologic measures of disease activity related to plasma viscosity (secondary endpoint) were not significantly different in patients receiving care from a rheumatology NP, compared to patients receiving care from junior hospital physicians[55] [Appendices I-2 and J]. Distinctions between NP interventions associated with statistically significant differences in physiologic marker endpoints, and those associated with non-statistically significant differences, point to these studies using different NP interventions on different study populations, with different control groups for different study durations. However, when results are not "statistically significant" it cannot be assumed that there was no impact.[88]

Symptom Severity, Functional Status, Behaviour / Lifestyle Change

More than half of this review's RCTs (18/29; 62%), including 4/10 post hoc analyses [Appendix I-3] measured 'symptom severity, functional status, or behaviour / lifestyle change.' While most of these studies focused on patients with chronic diseases, 'symptom severity, functional status, and behaviour / lifestyle change' were also assessed for NP interventions based in acute care, an NP intervention for breast cancer survivors, and for patients receiving an NP intervention post hip-fracture surgery. Ten out of 18 NP interventions were associated with at least one statistically significant difference in a 'symptom severity, functional status, and behaviour / lifestyle change' endpoint [Table 4],

and consisted of various combinations of NP activity domains: diagnosis, prescribing, clinical procedures, strategies for behaviour change / education, and care coordination [Table1].

Symptom severity was assessed in 15 RCTs. Most of these trials examined outpatient NP interventions where symptom severity was usually combined with functional status assessments. For example, in an IPT pilot trial that tested the benefits of an accessible pulmonary NP for outpatients with chronic obstructive pulmonary disease (COPD), symptom severity was measured according to the mean change in the Clinical COPD Questionnaire (CCQ) scores, alongside a functional status endpoint of time to first exacerbation.[50] Patients randomized to the NP intervention experienced slower deterioration over 24 months compared to usual care in the symptom domain of the CCQ (0.14, +/- 0.14 in the NP group versus 0.58, +/- 0.16 in usual care, $p = 0.04$), with the difference of 0.44 meeting the minimal clinically important difference (MCID) for the CCQ total score of 0.4 [Table 5]. However, no significant statistical impact was found in secondary endpoints of median time to first exacerbation ($p = 0.40$) or in the symptom domain of the St. George's Respiratory Questionnaire (SGRQ, $p = 0.10$), although the difference of 7.7 between groups on the symptom domain of the SGRQ did meet the MCID of 4 for the SGRQ total score[50] [Appendices I-3 and J]. Symptomology and functional status were assessed in outpatients with rheumatoid arthritis who were managed by a NP compared to a physician. Greater numbers of intervention than control patients showed improvement in the study's primary endpoint, the Disease Activity Score 28 (DAS 28, comprised of four measures: erythrocyte sedimentation rate related to inflammation, the patient's global assessment of disease, the number of tender joints, and the number of swollen joints using the 28-joint count), although no p-values were reported [Table 5]. Differences in the secondary endpoint of physical function, measured by the Arthritis Impact Measurement Scale (AIMS) were non-significant, yet a 67% improvement in the length of fatigue was found in intervention patients compared to control patients at 48 weeks study completion, with median values (range) of 60 minutes (0 - 600 minutes) in the NP group versus 270 minutes (0 - 600 minutes) in the control group, $p = 0.02$. However, measures of fatigue were based on self-reported data in the absence of a formal measurement tool, and data regarding the number of patients per group for comparison of the fatigue outcome were incomplete[55] [Appendices I-3 and J].

Three RCTs focused on the care of cancer outpatients. Two of these trials measured both symptomology and functional status,[53,61] while one trial measured symptomology alone.[52] A trial of daily telemonitoring by NPs to advanced cancer patients was associated with a 16% reduction in its primary endpoint of 'average pain ratings' on the Brief Pain

Inventory (BPI). Only nineteen percent of intervention patients, compared to 35% of control patients experienced average pain intensity (scored as > or = to 4 on the BPI) at 1 week, p = 0.02[53][Table 5]. A significant difference (p = 0.03) was also found in the 'physical function' component of the EORTC QLQC-30 tool (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire). All other secondary outcomes were non-significant, with functional impairment measured using the Karnofsky performance score, the Hospital Anxiety Depression Scale (HADS) and the Distress Thermometer[53] [Appendices I-3 and J]. Breast cancer survivors experiencing menopausal symptoms due to estrogen therapy discontinuation, were randomized to usual care or a NP intervention consisting of counselling and recommendation of non-estrogen therapies. Patients in the NP group experienced reduced symptoms of menopause, measured using a composite symptom scale (p = 0.0004) [Table 5], and improvements in the secondary endpoint of sexual functioning, measured using the Cancer Rehabilitation Evaluation System (CARES) Sexual Functioning Scale (p = 0.04)[61] [Appendices I-3 and J]. Finally, women who had undergone surgery for suspected ovarian cancer received regular NP supportive care in follow-up, including a psychiatric NP for patients in high emotional distress. Intervention effects on cancer-specific quality of life were measured at baseline (24 – 48 hours after surgery), one, three and six months post-surgery, using three different self-report questionnaires: the Center for Epidemiological Studies–Depression Scale (CES-D), the ambiguity subscale of the Mishel Uncertainty in Illness Scale (MUIS), and the Symptom Distress Scale (SDS).[52] In all three tools, reduced scores indicate reduced symptom severity. The effect of various combinations of oncology NP and psychiatric NP care on the rate of improvement in quality of life was examined using three types of mixed effect regression models: 1.(oncology NP intervention without psychiatric NP) $_{\text{oncology NP;}}$ 2.(oncology NP with psychiatric NP) $_{\text{oncology NP + psychiatric NP;}}$ and 3.(psychiatric NP separate from oncology NP) $_{\text{psychiatric NP}}$. All three models found that rates of improvement in 'uncertainty in illness' outcomes on the MUIS (reduced scores) were significantly greater for intervention patients than for control: effect estimate $_{\text{oncology NP}}$ = - 0.04847 ± se 0.01394 , p = 0.0006; effect estimate $_{\text{oncology NP + psychiatric NP}}$ = - 0.03917, ± se 0.00915, p < 0.0001; and effect estimate $_{\text{psychiatric NP}}$ = - 0.04978 ± se 0.02094, p = 0.0181.[52] Intervention patients' rate of reduction in symptom distress (SDS) was significantly greater than control when the psychiatric NP was analysed as a separate factor: effect estimate $_{\text{psychiatric NP}}$ = - 0.1164 ± se 0.01284, p < 0.0001. However, according to the CES-D tool, no significant rates of reduction in depressive symptoms were found for intervention patients in any of the three models [Table 5; Appendices I-3 and J]. Study authors suggested that anxiety

may be more reflective of existential concerns over time than depressive symptoms in women recovering from cancer surgery and undergoing chemotherapy.[52]

Depressive symptoms were measured in stroke survivors after psychosocial-behavioral sessions delivered by a NP.[54] Symptom severity was measured by the Hamilton Rating Scale for Depression (HRSD), alongside secondary measures of physical function, participation, and overall stroke impact, using the Barthel Index of Activities of Daily Living and the Stroke Impact Scale. While results for secondary measures were non-significant, depression levels were favourably impacted by nine psychosocial-behavioral sessions delivered by a NP over eight weeks, with mean HRSD scores (reduced scores better) of - 9.2 ± 5.7 intervention versus - 6.2 ± 6.4 control ($p = 0.023$) at 12 months. Throughout the trial, the percentage of patients in remission (i.e. HRSD < or = to 9) was greater for intervention patients than control patients. Differences were statistically significant at 9 weeks (OR = 4.8, CI 1.8 - 12.9, $p = 0.001$), 21 weeks (OR = 3.4, CI 1.3 - 8.7, $p = 0.008$) and 12 months (OR = 2.7, CI 1.1 - 6.6, $p = 0.031$); however, after 24 months of follow-up, the difference in remission rates was no longer statistically significant (NP 65% patients in remission vs usual care 46% patients in remission, $p = 0.13$). Patient contact in this trial was made either at patients' private homes or outpatient clinics, including rehabilitation facilities[54] [Table 5]. In contrast, the NP intervention for primary health care patients with incontinence occurred primarily within patients' homes. Statistically significant reductions were found in symptoms using a validated symptom severity questionnaire, and at three months, the percentage of patients reporting no symptoms or 'cured' was 25% in the intervention group and 15% in the standard care group (95% CI = 6 to 13, $p < 0.001$)[60] [Table 5]. Significant differences in 'improvement in one or more symptoms' were maintained in a long term follow-up study conducted six years later ($p = 0.02$)[81] [Appendix I-3].

Behaviour / lifestyle change relating to physical activity and diet were found in patients that received individualized NP management following coronary artery bypass surgery. Favourable effects were demonstrated at one year study completion for secondary endpoints of diet: total fat ($p = 0.009$), saturated fat ($p = 0.004$), cholesterol ($p = 0.006$); and physical activity (14% increase in metabolic equivalent (MET) hours per week compared to usual care, $p = 0.02$)[44] [Appendices I-3 and J]. Behaviour / lifestyle change was also assessed in obese patients. The lifestyle counselling intervention delivered by NPs led to significant weight loss among obese (BMI > or = to 30 kg/m^2) and moderately overweight (BMI 25 - 30 kg/m^2) patients, with percentage weight loss after one year significantly improved for intervention patients (mean change NP -1.9% (SD 4.9) versus GP -0.9% (SD 5.0), $p < 0.05$)[56]

[Table 5]. However, data stratified for obese and moderately overweight patients did not show statistically significant differences between groups. Nonetheless, significant reductions were found in waist circumference, with a reduction of 2.8 cm for men in the NP group compared to 0.9 cm in usual care, $p < 0.05$ [56] [Appendices I-3 and J]. Behaviour / lifestyle change was further assessed in two post hoc analyses of the lifestyle counselling intervention for obese patients, measuring one and three year effects respectively. At one year follow-up, an increase in walking of 33 minutes per week in the NP group compared to a decrease in walking of 5 minutes per week in the usual care group was observed ($p < 0.05$).[82] However, by three year follow-up, significant differences in percentage weight loss, waist circumference,[80] and physical activity[84] were not maintained. No significant differences were found in diet at both one and three year follow-up [82,84] [Appendix I-3]. Finally, behaviour / lifestyle change relating to rates of alcohol and drug use in low-income, young adult primary care patients was evaluated using the ASSIST (Alcohol, Smoking & Substance Involvement Screening Test) tool. Developed by the World Health Organization, this tool assessed the effectiveness of a brief motivational interviewing intervention conducted by NPs. Significant reductions in alcohol ASSIST scores were observed in the intervention group compared to usual care ($p = 0.0293$), while differences between groups for cannabis ($p = 0.1119$), and methamphetamines ($p= 0.2264$) were non-significant [Table 5].[68]

Symptom severity, functional status, and behaviour / lifestyle change endpoints were not consistently improved by NP interventions, with some interventions positively impacting certain endpoints but not others. For example, in the intervention targeting cardiac surgery outpatients, no significant differences were observed in the mean number of total symptoms between the intervention and control groups, measured by the validated Memorial Symptom Assessment Scale.[46] However, in another intervention targeting coronary artery bypass graft (CAGB) surgery outpatients, the overall mean scores measured by the validated 'Symptom Inventory,' showed a significant difference at two weeks (NP 45.2 (SD 10.2) versus usual care 50.4 (SD 12.6), $p = 0.002$), but by trial completion at six weeks, the significant difference did not persist ($p = 0.23$)[48] [Appendices I-3 and J]. In other cases, no significant differences were detected on these outcomes overall. A six-month intervention by a geriatric NP for post-surgical hip fracture outpatients resulted in no statistically significant differences between groups for self-rated health, level of depression, activities of daily living (ADLs), or instrumental ADLs (IADL), using the Global Health self-ratings, Geriatric Depression Scale and Functional Status Index respectively. However, this pilot trial's sample size was only 33

patients, with 10 patients lost to follow-up: four patients withdrew (three control and one treatment) and six died (three from each group) [Table 5; Appendices I-3 and J].[64]

Symptom severity and functional status were also measured in several RCTs using RS designs. In these studies, non-significant differences may be considered a positive result considering the comparator groups were typically managed by established providers. For example, measures of eczema severity (secondary endpoint, Appendices I-3 and J) in children using SCORAD (SCORing Atopic Dermatitis); and disease-specific quality of life (primary endpoint, Table 5) for children aged < or = to 4 years according to the Infants' Dermatitis Quality of Life Index (IDQOL), and for children aged 4 -16 years according to the Children's Dermatology of Life Quality Index (CDLQI), were not significantly different for patients receiving care from a NP or a dermatologist.[59] A NP intervention on an internal medicine hospital ward detected no statistically significant differences in measures of functional status, activities of daily living, symptom severity, and patient assessments of care, compared to regular house staff care. However, this trial's post-randomization breach resulted in crossover of 89 NP patients to the house-staff ward, with only 104 patients admitted to the NP ward after randomization of 193 patients to the NP ward, suggesting possible selection bias[71] [Appendices G, I-3 and J].

Another acute care RS trial compared care delivered by an emergency department NP for patients with soft tissue injuries to care provided by extended scope physiotherapists (ESPs) and doctors. Non-significant differences were detected in primary measures of functional recovery outcomes, using the "Disability of the Arm, Shoulder and Hand" score for upper-extremity injuries, and the "Lower Extremity Functional" score for lower-extremity injuries[63][Table 5]. Symptoms of swelling and stiffness in minor injury patients treated either by a NP or a senior house officer in an emergency department, were measured in a one month follow-up questionnaire, alongside functional status in terms of time to recovery, level of activity, sleep patterns, and productivity (time off work). Again, differences in symptoms and functional status between minor injury patients in intervention and control groups were all non-significant.[62] Finally, differences in secondary measures of peak flow were not significantly different between acute asthma outpatients managed by NPs or respirologists[49] [Appendices I-3 and J].

Drug Utilization

The impact of NP interventions on drug utilization was measured in 8/29 studies (28%) [Appendix I- 4]. Statistically significant differences were associated with four interventions, in terms of 1) appropriate prescribing of inhaled corticosteroids for asthma,[8] 2)

reduced chronic oral non-steroidal anti-inflammatory drug (NSAID) use for chronic musculoskeletal pain,[66] 3) administration of medications for treatment of soft tissue injury in an emergency department,[63] and 4) target use of beta-blocker medication for chronic heart failure patients.[45]

A NP intervention comprised of expanded prescribing provisions within an educational outreach program, sought to improve the case management of respiratory disease patients in primary health care clinics in South Africa. However, the intervention's impact on anti-infective / anti-inflammatory drug utilization for tuberculosis, tuberculosis / HIV co-infection, upper / lower respiratory tract infection, asthma, and chronic obstructive pulmonary disease was inconsistent. For example, NP care increased the use of inhaled corticosteroids (outreach 13.7% (137/1000) versus control 7.7% (77/999), OR 1.90, 95% CI 1.14 to 3.18, p = 0.006, ICC = 0.019), while no statistically significant differences were observed for co-trimoxazole use in patients with HIV, or in antibiotic prescribing overall.[8] Results for utilization of antibiotics were similar between groups, with 39.7% (397/1000) of outreach patients versus 39.4% (394/999) control patients receiving prescriptions (OR 1.01, 95% CI 0.74 to 1.38, p = 0.95, ICC = 0.042). However, the lack of change in antibiotic prescribing may well be appropriate for the severe case mix comprising the study population. Within the subset of 'patients with predefined markers of severe diseases,' more referrals to physicians occurred at intervention clinics[8] [Table 5].

An intervention delivered by a single NP to five different primary health care clinics targeted patients with non-malignant, non-inflammatory musculoskeletal pain who regularly used non-steroidal anti-inflammatory drugs (NSAIDs). The six month NP intervention consisted of individualized strategies to reduce NSAID use (e.g. strategies on weight reduction, exercise, relaxation, etc.). Reduced NSAID use was this study's primary endpoint, measured with a self-administered questionnaire that was validated with computerized prescription records.[66] In the intervention group, 38% (42/110) had either discontinued or reduced their NSAID dose by ≥ 50% compared to 12.5% (14/112 patients) of the control group ($p < 0.0001$).[66] However, this self-reported endpoint was inevitably influenced by the element of 'social desirability,' where the active intervention provided advice for reduction of NSAID use[66] [Table 5].

Drug utilization in treatment of soft tissue injury was examined as a secondary endpoint in a RS trial based in an emergency department, where medication use between three groups of professionals (NPs, extended scope physiotherapists, and doctors) was reported as administered to 23.5% of all participants, although no raw data is shown.[63] The

extended scope physiotherapist (ESP) group administered medication to 3.6% of patients, compared to 23.2% for NPs and 42.2% for doctors ($p < 0.001$). Interpretation of this difference is complicated by the lack of information underlying this result. While actual numbers of treatments appeared to differ significantly (data not shown), practitioners were reported to be clinically equivalent[63] [Appendices I- 4 and J].

Adjustment of medication was measured in three IPT interventions targeting outpatients with cardiovascular disease (CVD).[44,45,47] Utilization of beta-blocker medications was significantly improved by a NP intervention in chronic heart failure outpatients receiving either usual care, electronic prescriber notifications, or NP facilitation, with the proportion of outpatients reaching target doses of beta-blocker medication measured as a primary endpoint.[45] In the NP facilitator group, 67% (36/54) of patients were either initiated or up-titrated on beta-blockers, compared to 16% of the notification group (10/64) and 27% of the usual care group (14/51), $p < 0.001$.[45] Also, more subjects in the NP facilitator group reached target doses compared to control and notification groups: 43%; 23/54 versus 10%; 5/51 and 2%; 1/64 respectively, $p < 0.001$.[45] Further, among patients who reached target doses of beta-blockers, the mean length of time from initiation to target dose was also lowest in the NP facilitator arm (5.9 months), compared to the control group (8.5 months) and the notification group (9.3 months), $p < 0.001$[45] [Table 5].

A RCT of patients with four types of established cardiovascular disease (CVD): peripheral arterial disease, abdominal aortic aneurysm, cerebrovascular disease, and coronary heart disease, compared usual care to 'NP management of risk factors in addition to usual care.'[47] Self-reported use of medications after one year (antiplatelet agents, blood pressure-lowering agents, lipid-lowering agents, glucose-lowering agents, ACE-inhibitors / angiotensin II antagonists, and folic acid) was measured as a secondary endpoint, while the primary endpoint was the achievement of treatment goals in physiologic CVD risk factors.[47] A NP helped patients develop action plans that included aspects of lifestyle and medication, following a protocol for each risk factor. At one-year follow-up, medication use increased in both groups, but more so in the intervention group for five out of six types of medication. However, the study physician was required to prescribe or change medication during the trial, since a NP was not formally allowed to prescribe in the Netherlands. While study authors did not report p-values for these self-reported measures, the largest differences were noted in the utilization of lipid lowering drugs, ACE-inhibitors / angiotensin II antagonists, and folic acid. Lipid lowering drugs were used by 89% (80/90) NP patients versus 73% (55/75) usual care patients; ACE-inhibitors / angiotensin II receptor antagonists, by 76% (57/90) NP patients

versus 53% (40/75) usual care patients; and folic acid was used by 61% (55/90) NP patients versus 28% (21/75) usual care patients. Glucose-lowering agents were used by 19% (17/90) NP patients versus 16% (12/75) usual care patients, blood pressure lowering agents by 77% (69/90) NP patients versus 69% (52/75) usual care patients, with virtually identical use of antiplatelet agents by 90% (81/90) NP patients versus 91% (68/75) usual care patients[47] [Appendices I-4 and J].

Non-significant differences in drug utilization were detected in a study of patients who had received coronary revascularization surgery, followed by a NP intervention comprised of 'individualized case management of cardiovascular risk factors in addition to usual care.'[44] Four to six weeks following cardiac surgery, the need for / adequacy of drug therapy was evaluated by the NP according to lipid management algorithms. Medication was initiated or adjusted at a serum concentration of low-density lipoprotein cholesterol (LDL-C) > 2.20 mmol/L, with patient progress periodically assessed through plasma lipid and liver function tests. When the response to drug therapy was adequate, the patient was retested every three months, or more frequently for drug combinations requiring closer follow-up. Part of the NP intervention also included lifestyle modifications, including nutritional counseling and exercise plans, which were emphasized as an integral part of lipid management in conjunction with pharmacotherapy. At one year, eighty-seven percent (100/115) of patients in the NP group and 79% (89/113) of patients in the usual care group were on lipid-lowering drugs, $p = 0.1$.[44] Among patients on pharmacotherapy, 97% in both groups were taking a single statin agent (HMG coenzyme A reductase inhibitor)[44] [Appendices I-4 and J]. As discussed previously, non-significant differences in RS studies can be interpreted differently than those for IPT studies. For example, a RS study compared care provided by a single NP with over 20 years of rheumatology experience to traditional care provided by Junior Hospital Doctors (JHDs) two years into their rheumatology training rotation. No significant differences were observed in the use of intra-muscular steroids at 48 weeks: NP 15% (36/234) versus JHD 13% (29/226). Medication changes on consult with the study rheumatologist were also similar between both practitioners: NP 24% (56/234) versus JHD 22% (50/226) [55] [Appendices I-4 and J].

Using a similar RS design, patients in primary health care clinics were randomized to newly graduated NPs or GPs with an average of about 16 years' experience. The numbers of prescriptions given for respiratory / throat infections, ear infections, and urinary tract infections at primary health care clinics were not significantly different for endpoints of one prescription given (NP 55.0% (411/747) versus GP 54.2% (352/650), $p = 0.75$), two

prescriptions given (NP 16.9% (126/747) versus GP 19.5 % (127/650), p = 0.20), or three or more prescriptions given (NP 8.8% (66/747) versus GP 7.8% (51/650), p = 0.51). However, set in the Netherlands in the year 2009, NPs in this RCT had no full authority to prescribe medications, such that GPs validated the NPs' prescriptions. As a result, substantial confounding by the physician's role cannot be ruled out[67] [Appendices I-4 and J].

4.6.3 Resource Utilization / Cost Endpoint-Outcomes

Fourteen RCTs contained at least one measurement of resource utilization or cost.[6,46,48-50,55,60,62,63,65-67,69,71] Resource utilization / cost was evaluated in separate post hoc publications for six interventions[27,78,79,81,83,86] [Appendices I-5 – I-7]. Endpoints under this category primarily focused on hospital care (emergency department visits, inpatient admissions, length of stay, readmission to hospital, hospital lab tests), but also included outpatient visits (visits to outpatient clinics, specialist consultations), family practice visits in the primary health care setting, and various associated costs. Whether set in primary health care, outpatient settings, or acute care, trials measuring resource utilization / cost virtually all evaluated acute care resources (12/14 RCTs).[6,46,48-50,55,60,62,63,65,69,71] However, only 3/29 (10%) of this review's RCTs were actually set in acute care,[62,63,71] with all three acute care RCTs designed as RS trials, to compare the effectiveness of two or more different types of health care providers.

Controversy accompanied appropriate approaches taken to cost analyses of equivalence trials, designed to show that two interventions do not differ in either direction ('zone of indifference' regarding superiority / inferiority) by more than a pre-specified insignificant amount (i.e., a two-sided test).[85] Two RS trials of this review used cost minimization analysis,[27,86] a method considered rarely appropriate for evaluation of cost for health effects.[91] The premise for this method is that the intervention and control treatments are equally effective yet few interventions are actually equally effective. Evidence must support the claim that outcomes are the same enabling an analysis of costs only, with the least costly alternative considered the most efficient.[91] In terms of categorization of costs for analysis, the Panel on Cost-Effectiveness (CE) in Health and Medicine further asserts it is uncontroversial for cost-effectiveness analyses (CEAs) informing societal resource allocation to include societal costs. Health intervention studies informing societal resource allocation are to include resource costs from a long-term, societal perspective, where the numerator of a CE ratio captures changes in resource use associated with an intervention while the denominator captures changes in health associated with an intervention. The societal

perspective dictates that all impacts on human health and resources must be included in either the numerator or denominator of a CE ratio to avoid incomplete analyses.[92]

Acute Inpatient Care

All three RCTs set in acute care were RS trials that measured resource utilization, but only one statistically significant between-groups difference was found, in wait times for minor injury patients treated by NPs and senior house officers.[62] The average wait for each practitioner at this study's emergency department (ED) was 70.1 minutes for the senior house officer (n=102) compared to 48.6 minutes for the NP (n=102), (95% CI 11.2–31.8 min, $p < 0.001$)[62] [Table 5]. Although cost was not measured, cost implications include costs of professional service time and costs of the patient's time spent waiting, in terms of productivity loss and personal payment for health care. Differences between groups in resource outcomes of total consult time, seeking advice, X-ray requests, referral to follow-up clinics, unplanned follow-up, and missed injuries, were not statistically significant[62] [Appendices I-5 and J]. A trial set in an inner city emergency department (ED), measured functional recovery to the injured extremity as its primary endpoint, to evaluate clinical effectiveness of three ED professionals: NP, ESP (extended scope physiotherapist) and doctor. Number of days off work was reported as a secondary outcome in this trial, with care provided by NPs and ESPs reported to be equivalent to routine care provided by doctors.[63] In the post hoc economic evaluation that employed the method of cost minimization analysis on the premise that the three groups of ED professionals were clinically equivalent,[63] the cost of NP care was found equivalent to routine care, while ESPs were either equivalent or cheaper. Both ESPs and NPs were found to incur greater indirect costs associated with follow-up appointments. However, limitations to endpoint assessment included no verification of self-reported time spent with patients by each professional group, time upon which calculations were based, resulting in estimates that may not be robust[86] [Appendices I-5 and J]. NP care for general medical inpatients was assessed for length of hospital stay, number of consultations to other services, hospital charges, and overall costs, compared to traditional house staff. Only non-significant differences were detected, with NPs incurring higher pharmacy and lab costs, shorter length of hospital stay, smaller total and ancillary hospital charges, lower costs in radiology and respiratory therapy, less transfers to intensive care units and less hospital acquired complications ($p > 0.1$)[71] [Table 5].

Specialized Outpatient Care

Ten NP interventions from the outpatient setting were evaluated for their impact on resource / cost endpoint-outcomes, seven within the original trial,[6,46,48-50,55,65] and three

resource / cost evaluations occurring post hoc to the original trial.[78,79,83] Statistically significant differences were detected in five interventions, two of which were reported in post hoc analyses.[78,79] However, eight out of 10 outpatient studies used endpoint assessment tools of limited quality, based on estimations of health care utilization according to patient self-report in the absence of a tool formally tested for reliability / validity [Appendix I-6]. Two RCTs of respiratory disease measured outpatient resource use, one a RS trial evaluating care provision for acute asthma patients,[49] and the other an IPT trial testing a patient-initiated strategy for care of chronic obstructive pulmonary disease (COPD) patients.[50] In the RCT of acute asthma patients, resource measurements included hospital clinic attendance; visits to general practice offices, emergency departments, or ambulance paramedics for exacerbations; and hospital readmissions.[49] The mean number of follow-up clinic appointments attended was 1.97 in the NP group (130 clinics /66 patients) versus 2.23 in the doctor group (147 clinics /66 pts), with a statistically significant relative risk of 0.88 (95% CI 0.70 to 1.12), p = 0.011. Differences in resource use for exacerbations were non-significant, e.g. relative risk of hospital readmission = 0.40 (95% CI 0.14 – 1.12, p = 0.09)[49] [Appendices I-6 and J].

An on-demand strategy of outpatient-scheduling for COPD patients was tested in an IPT trial where patients were instructed to call the pulmonary NP on an increase of symptoms. Subsequent costs were calculated in relation to the number of visits to GPs, pulmonologists, pulmonary NPs, and hospitals. GPs and pharmacists were contacted to collect healthcare resource use in primary care while the hospital's computer system was used to identify visits to pulmonologists, pulmonary NPs and emergency rooms. Costs were then evaluated from two perspectives: healthcare provider (GP, pulmonologist, and pulmonary NP as outpatient providers; emergency department and pulmonary ward as inpatient providers), and healthcare insurance costs for all aforementioned providers.[50] In primary care, reductions in GP visits for COPD were found to be statistically significant in the on-demand versus control group: median score with range NP 4 (0-32) versus GP 5 (0-20), p = 0.01. The number of visits to the pulmonary NP increased significantly in the on-demand versus control group: median score with range NP 1 (0-14) versus Doctor 0 (0-4), p = 0.003, while no statistically significant differences were detected between groups for exacerbations, visits to the pulmonologist, and hospitalizations.[50] Total costs were lower in the intervention group, owing in part to the slower COPD deterioration in the NP group, reflected in the statistically significant differences in the symptom domain of the Clinical COPD Questionnaire (section 4.6.2). Although total costs were lower for the on-demand group from both perspectives: 1) healthcare provider (mean savings of € 518 per intervention

patient) and 2) healthcare insurance / reimbursement (mean savings of € 458 per intervention patient), these lower costs were not statistically significant[50] [Appendices I-6 and J]. NP support to outpatients following surgery for suspected ovarian cancer did not result in significant differences in the number of self-reported hospitalizations, emergency room or oncology outpatient visits. However, based on regression modelling, primary health care visits were estimated to be lower in the NP group, with statistically significant differences in estimated effect sizes: NP 1.58 (n = 59) versus control 2.45 (n = 62), p = 0.0003[79] [Appendix I-6].

Another RCT examining resource use of patients immediately following their hospital discharge, tested the effect of a 'brief NP intervention' on older adults transitioning home, in terms of ED visits, hospital admissions, days hospitalized, and number of physician office visits.[65] Patients randomized to the NP intervention group had significantly fewer physician office visits throughout the six month study duration: NP (n=100) mean 9.94 (SD 8.5) versus usual care (n=99) mean 11.72 (SD 7.7), p = 0.036. However, no significant differences were observed for ED visits (NP mean 0.50 (SD 1.2) versus usual care mean 0.99 (SD 2.5), p = 0.096), days spent in the hospital, home health care days of service, or hospital re-admissions [65] [Appendices I-6 and J]. The only other statistically significant difference found in resource / cost endpoints of outpatient studies, compared care provided by NPs and dermatologists to children with eczema and their families.[59] This trial's post hoc cost-effectiveness analysis (CEA) included costs measured from a societal perspective as well as a current report on international costs of eczema in children, for accurate comparison with costs in the present study.[78] The mean annual family costs / patient were significantly higher at €608 in the dermatologist group compared to €302 in NP group (mean difference - €306, 95% CI - €475 to - €16), with treatment of mild, moderate and severe levels of eczema, incurring higher mean annual healthcare costs in the dermatologist group than in the NP group, by €427, €314, and €315 per child respectively. Lower costs in the intervention group were largely due to the lower salary of the NP combined with a lower number of outpatient visits in children aged < 4 years in the NP group. Also, patients randomized to NP care had fewer GP visits in the follow-up period compared to those managed by a dermatologist[78] [Appendix I-6].

In five outpatient RCTs, no significant differences were detected / reported in resource utilization / cost endpoints. Three of these interventions consisted of risk factor management in post-surgical cardiovascular disease (CVD) patients, one consisted of web-based blood glucose management in type two diabetes patients, and the other consisted of an intervention designed to test substitution of a rheumatology NP for junior house doctors

(JHDs) in outpatient care of rheumatoid arthritis patients. Two RCTs of post-cardiac surgery outpatients evaluated the effect of NP support in addition to usual care, on emergency department visits and hospital admissions, tracked through patient self-report.[46,48] Non-significant differences in healthcare resource use were found by outpatients who underwent coronary artery bypass grafting, with the control group self-reporting higher totals of 7 more emergency department (ED) visits and 4 more hospitalizations by six week study completion than the intervention group. Study authors noted potential clinical significance, based on less physician visits, ED visits, and hospital readmissions overall for intervention patients than for control patients.[48] The other RCT of cardiac surgery outpatients tracked patient flow for five weeks following hospital discharge and found non-significant differences in the other direction, with ED visits self-reported for 23% (21/92) intervention patients versus 16% (15/92) control patients ($p = 0.36$), and hospital readmissions self-reported for 9.8% (9/92) intervention patients versus 8.7% (8/92) control patients, $p = 0.85$ [46] [Appendices I-6 and J].

A short term economic evaluation was undertaken to determine if a NP intervention focused on cholesterol management in high risk coronary heart disease patients,[44] justified the additional costs associated with the expanded service provision.[83] This was not a comprehensive cost-effectiveness analysis (CEA) that considered savings associated with the prevention of cardiovascular events by assuming the societal perspective, but a CEA that only provided a basic understanding of the cost-effectiveness of NP case management for reduction in low-density lipoprotein cholesterol (LDL-C) levels.[44] The annual incremental cost of NP case management of hypercholesterolemia was $26.03 per mg/dL and $39.05 per percentage reduction in LDL-C.[83] Despite less NP time required for patient management over time, these time-savings were offset by more expensive, escalating drug treatment in most patients. As a result, the significant reduction in LDL-C among intervention patients, was not attained within the range of cost-effectiveness anticipated when compared to control[83] [Appendix I-6]. Delivering an NP intervention through a web-based platform may generally be expected to reduce costs of patient management. However, the NP intervention designed to manage patients' type two diabetes was associated with non-significant differences in measures of resource utilization, including visits to primary care clinics, outpatient clinics, specialty physician offices, and inpatient days during a two year period. Yet this IPT web-based RCT for type two diabetes patients was only powered to test its hypothesis on the physiologic marker of glycated hemoglobin.[6] Finally, a RS intervention for rheumatoid arthritis outpatients found lower numbers of lab tests, X-rays, and GP visits in the NP group

compared to control, although 20% more referrals to other health professionals were made in the NP group (no p values reported)[55] [Appendices I-6 and J].

Primary Health Care

Resource utilization / cost endpoints were assessed for four NP interventions delivered from primary care settings,[60,66,67,69] including two post hoc analyses[27,81] [Appendix I-7]. Cost assessments specifically, included a cost minimisation evaluation of NP substitution for GPs,[27] as well as two cost-effectiveness analyses (CEAs): one of a continence service (home care)[60] and another of its long term follow-up study.[81] Although three interventions were associated with statistically significant results, all endpoint assessments were of limited to low quality. In a RCT comparing NPs to GPs in primary health care clinics, resources were evaluated according to duration of consultations, patient outcomes (return visits; productivity losses), and medical resource consumption (diagnostic procedures), with no report of acute care utilization in this trial.[67] The number of prescriptions issued were tracked as a measure of medical resource consumption rather than drug utilization per se [Appendix I-4]. Statistically significant between-group differences included longer face-to-face consults with patients, with NPs at 12.22 minutes (SD = 5.7) versus GPs at 9.20 minutes (SD = 4.8), $p < 0.001$, and more frequent re-attendance of NP patients than GP patients, with a difference of 5.2% ($p = 0.04$). Patients' productivity losses were reported to be identical at a mean value of 1.11 days. No statistically significant differences between groups were found in the percentage of prescriptions given, whether one ($p = 0.75$), two ($p = 0.20$), or three or more ($p = 0.51$) prescriptions were given; nor in the investigations ($p = 0.55$) or referrals ($p = 0.24$) carried out. However, neither was there any conclusive properties-information reported for the study questionnaires that provided data for group comparisons, but only a justification of validity according to the study authors' assurance on discussion with two GPs with research experience[67] [Appendix I-7]. In the post hoc economic evaluation of this trial, costs of GP versus NP consultations were estimated from practice and societal perspectives.[27] Direct costs were significantly lower for consultations by NPs versus GPs, with a mean difference of €8.21 per consultation ($p = 0.001$).[27] Overall direct costs (resource use, length of consultations, costs of follow-up consultations, and salary costs) were also significantly lower in study clinics that integrated NPs, compared to control clinics that did not integrate NPs, with a mean difference in direct costs of €3.45 per consultation in favour of study clinics (NP or GP consultations), $p = 0.04$.[27] Cost differences were mainly caused by the difference in salary between NPs at €41,160.00 per year and GPs at €94, 475.92 per year (p.e30) [27] [Appendix I-7].

The only other RCT in this review that measured resource / cost endpoints that were not based in acute care, involved an NP intervention providing advice for reduction of non-steroidal anti-inflammatory drug (NSAID) use in patients with chronic musculoskeletal pain.[66] Resource utilization was measured in terms of i) costs of the NP-based educational service, including clinic / home visits; and ii) patient costs, including travel and time for appointments with the NP, excluding costs incurred by patients resulting from the advice given (e.g. additional purchases of drugs and equipment such as hot and cold packs / wraps, posture support braces, specialized footwear etc.). However, outcome assessment for both groups was based on treatment by the same single NP, with changes in health service use, drug and patient costs all self-reported, and not inclusive of all (societal) costs.[66] The NSAID study is the only study in this review that focused on the discontinuation of medications. Chronic NSAID users' prescription costs were significantly lowered in the intervention group compared to control. Forty-two (38%) intervention patients either stopped taking oral NSAIDs altogether or reduced their dose by 50% or more, compared to 14 (13%) control group patients ($p < 0.0001$) [Appendix I-4]. Although this trial found a significant reduction of 2.61 British pounds in median NSAID costs for intervention patients over six months ($p = 0.008$), a non-significant increase in total prescription costs occurred in both groups, to a larger degree in the intervention group. The overall mean cost of the NP intervention was calculated to be £40.70 per patient, with no known comparator value provided for standard GP service. Mean patient travel costs were reported as £0.83 per patient, with no comparative control cost provided [66] [Appendices I-7 and J].

Resource utilization and cost endpoints were evaluated in a RS trial of low-income mothers and infants during the first two months post-partum. A NP intervention comprised of six follow-up phone calls on post-hospital discharge days 3, 7, 14, 21, and months 1 and 2, screened for concerns and offset challenges such as language barriers and sparse social support that could impede health care access. Usual care was comprised of information taken home on hospital discharge, and a pediatrician appointment at two months.[69] Investigators quantified the costs for infants' emergency department visits, urgent-care-centre visits, or re-hospitalisations, at two months post-hospital discharge. Intervention costs included estimations of NP services based on the time required for phoning patients, charting / filing, consulting with physicians, as well as administration time.[69] Where the intent of this RCT was to provide a comparison of health care charges between groups, distinctions were thus noted by the study authors in terms of health care charges being inequivalent to comprehensive costs that include societal costs. Health care charges associated with the

intervention infants' emergency room visits, urgent-care-centre visits, or re-hospitalisations, as well as charges associated with the intervention service at two months post-discharge, resulted in total intervention group charges of $14,333, compared to $70,834 for the control group, a difference of $56,501, $p < 0.05$. In addition to the study authors' acknowledgement that this RCT does not provide a formal cost comparison inclusive of societal costs, further perspective is noted in the small sample size of this trial, resulting in a cost differential that was largely comprised of the difference in hospitalizations (one hospitalization in the intervention group vs three hospitalizations in the control group)[69] [Appendices I-7 and J].

Finally, resource / cost evaluation of a NP-led continence service was made based on patient interviews regarding contacts with National Health Service providers for urinary symptoms and use of consumables (incontinence supplies and prescription medicines), at six months[60] [Appendix J] and at six-year follow-up[81] [Appendix I-7]. However, while costs of usual care services were taken from published national cost data, costs of the intervention service were only estimated based on a 'home care' service model, with in-home interviews conducted at baseline, three, and six months. Intervention patients that received the NP-led service reported higher cost and lower cost-effectiveness at six months for symptom reduction.[60] Patients were included in the cost-effectiveness analysis (CEA) only if full costs and number of symptoms alleviated could be calculated at both the three and six-month home interview, resulting in only 905/3746 or 24% of the total group of study patients completing resource data for the CEA: 734 patients from the intervention arm and 171 from the standard care arm (individual randomization occurred at a ratio of 4:1 for NP patients: usual care patients, in order to ensure sufficient numbers of intervention patients for evaluation of symptoms).[60] Not accounting for 76% of the total participants, 81% (734/905) of the patients that provided data for the CEA were intervention patients while 19% (171/905) of the patients that provided data for the CEA were standard care patients.[60] While the quality and validity of a CEA depend crucially on the quality of the underlying data that describe the effectiveness of interventions and the course of illness without intervention,[92] neither the original incontinence trial[60] nor the long-term follow-up[81] tabled any stratification of cost (only the distinction between National Health Service costs and individual costs, with reference to an online Supplementary Table 4 that is no longer available). In the long term follow-up study, costs in the NP arm were again reported higher than those in the standard care arm, although these differences in cost were not statistically significant[81] [Appendix I-7].

4.6.4 Global Quality of Life / Patient Satisfaction Endpoint-Outcomes

Global Quality of Life

Quality of life endpoints were measured in 9/29 (31%) trials [Appendix I-8]. All quality of life measurements were made by the reliable and valid SF-36 tool (or the shorter 12 and 8 item versions), providing information regarding non-specific, overall functional health and well-being from the patient's point of view.[93] Overall / global quality of life (versus disease-specific quality of life, noted in 'symptom severity' of section 4.6.2) was measured for several different types of NP interventions targeting patients with chronic disease, remitted breast cancer, chronic musculoskeletal pain, as well as hospitalized patients.

Only one RCT detected statistically significant intervention effects on global quality of life outcomes, in women recovering from surgery for suspected ovarian cancer. Significant results were revealed in regression modelling, used to evaluate the effect of various combinations of oncology NP and psychiatric NP (PSYNP) care on patients' rate of change in global quality of life (QOL) over time, compared to control.[52] This trial used the SF-12 tool to measure global QOL (higher scores indicate better health) alongside measures of cancer-specific QOL, reported earlier in section 4.6.2. The rate of improvement over time in both physical and mental components of the SF-12 were reported as 'estimated effect' values derived from the model, with each of three models built to reflect the variable assignment of the PSYNP for women in the intervention group in high emotional distress: 1) the PSYNP component significantly increased the rate of improvement over time in both physical and mental components of the SF-12: a) physical effect estimate = 0.1948 ± se 0.03877, $p < 0.0001$ and b) mental effect estimate = 0.06558 ± se 0.01676, $p = 0.0001$; 2) the oncology NP without the PSYNP resulted in less favorable significant differences in the physical SF-12 score: effect estimate = - 0.07599 ± se 0.02425, $p = 0.0019$, with non-significant differences in the mental SF-12 score: effect estimate = 0.01776 ± se 0.01138, $p = 0.1195$; and 3) the oncology NP and PSYNP components analysed together found a significant difference in mental SF-12 scores: effect estimate = 0.02300 ± se 0.00748,

$p = 0.0023$, while study authors reported a poor model fit related to the physical component of the SF-12[52] [Table 5, Appendices I-8 and J].

The remaining eight RCTs did not detect significant differences in global QOL. Two of these trials employed a RS design: one compared care delivered by NPs, extended scope physiotherapists and physicians for emergency department patients with soft tissue injuries,[63] and the other compared care delivered by NPs to that provided by regular house-staff for acute internal medicine patients;[71] in both cases, no significant differences in global QOL

were detected. In addition, the six IPT trials that did not detect statistically significant differences in global quality of life outcomes included three outpatient interventions that focused on patients with cardiovascular disease,[46-48] a NP intervention providing on-demand care for COPD patients,[50] NPs providing symptom management to breast cancer survivors,[61] and the intervention for reduction of chronic oral non-steroidal anti-inflammatory drug (NSAID) use in patients with chronic musculoskeletal pain[66] [Appendix I-8].

Patient Satisfaction

Patient satisfaction endpoints were measured in 8/29 (28%) trials and one post hoc analysis, with statistically significant improvements observed in seven out of eight trials [Appendix I-9]. However, none of these studies measured patient satisfaction as a primary endpoint [Appendix J]. A RS trial that compared care of minor injury patients by NPs or senior house officers (SHOs) at an emergency department, found significant differences in four out of eight measures of patient satisfaction.[62] Each patient was asked to complete the satisfaction questionnaire immediately after their treatment and prior to leaving the emergency department. Although there was no combined summary score, the eighth question asked of overall patient satisfaction. Significant differences were found in the following questions: NPs were easy to talk to (NP 97.6 (n=85) versus SHO 84.0 (n=81), $p = 0.009$), patients were given information on accident and illness prevention (NP 75.3 (n=81) versus SHO 45.2 (n= 73), $p = 0.001$), patients were given enough information on their injury (NP 95.2 (n=83) versus SHO 82.5 (n=80), $p = 0.007$), and overall, patients were more satisfied with treatment provided by NPs than by SHOs (NP 98.8 (n=85) versus SHO 87.7 (n=81), $p < 0.001$). Differences between groups regarding the patient feeling able to ask questions, understanding advice received, feeling that the providers listened and gave enough time, were all non-signficant[62] [Appendices I-9 and J].

In the outpatient setting, coronary artery bypass graft (CABG) patients were found to be more satisfied with NP follow-up than usual care at two and six week time points, according to two questions from the Client Satisfaction Questionnaire (CSQ-8, a four point Likert-scale questionnaire; higher scores represent higher levels of satisfaction): 1) 'quality of service' received at two weeks, $p = 0.003$, and at six weeks, $p = 0.005$; and 2) the 'amount of help' received, at two weeks, $p = 0.001$, and at six weeks, $p = 0.002$ (individual data not shown).[48] The other RCT of cardiac surgery outpatients treated by a NP phone intervention, used a questionnaire developed by Shortell et al. (2000) consisting of 24 closed-ended questions regarding patients' perceptions of their hospital care, returning home issues, and related heart patients' needs. Out of seven patient satisfaction measures within the five-week

post-discharge intervention, one statistically significant outcome and one borderline significant outcome were observed respectively: higher satisfaction in 'achieving best recovery possible' (NP 71.3% (n=102) versus usual care 63.5% (n=98), p = 0.03) and higher satisfaction with 'side effect information' (NP 61.5% (n = 102) versus usual care 54.0% (n=98), p = 0.05). While five out of seven measures of post-discharge patient satisfaction yielded non-significant results, all differences were in the direction of the intervention. However, the pooled score of mean percentages for patient satisfaction with recovery at the end of five weeks post-hospitalization was non-significant with NP 60.5% (20.4) versus usual care 55.7% (20.8), p = 0.08[46] [Appendices I-9 and J].

Two additional outpatient RCTs, both RS, found statistically significant differences in patient satisfaction outcomes. Parents ranked patient satisfaction with care provided by a NP and dermatologist for infants and children with eczema, using the Client Satisfaction Questionnaire-8 (CSQ-8, higher scores represent higher levels of satisfaction). Parents of infants and children with eczema who received treatment from a NP, were significantly more satisfied than those receiving usual dermatologist care, at all time points: 4 months (NP 27.1 (3.9) versus usual care 24.4 (3.4), p < 0.001); 8 months (NP 27.3 (4.0) versus usual care 24.3 (3.3), p < 0.001); and 12 months, (NP 26.9 (4.9) versus usual care 24.8 (4.3), p < 0.023).[59] For rheumatoid arthritis patients, overall patient satisfaction increased significantly for NP patients while remaining relatively stable in patients cared for by Junior House Doctors (JHDs). Median values with range for overall patient satisfaction were: NP baseline 3.57 (2.3 - 4.9) to 48 weeks 4.1 (2.4 - 4.9), difference of = 0.53, versus JHD baseline 3.60 (2.1 - 4.8) to 48 weeks 3.56 (2.4 - 4.7), difference of = - 0.04, between groups p < 0.001.[55] A pilot trial that was designed to assess its 'Brief Nurse Practitioner Transition' (BNPT) intervention for older adult outpatients transitioning home from hospital, found no significant differences compared to usual care provided by the Health Maintenance Organization (HMO). This trial's 'Home Care Satisfaction Measure' evaluated older adults' level of involvement in health care decision making, information / education received, emotional support, coordination / continuity of care, problem solving, and overall quality of care[65] [Appendices I-9 and J].

Interventions from two RCTs set in primary health care, one RS and one IPT, were both associated with statistically significant differences in patient satisfaction, although in both cases, tools used for endpoint assessment were of limited quality. The RS trial that compared care provided by NPs and GPs for patients with common complaints, measured patient satisfaction using a tool comprised of 12 items, partly derived from a validated

instrument (Wensing et al. 1997) as well as a questionnaire developed for patients seeking 'same day' consultations (Kinnersley et al. 2000). However, the content validity of this questionnaire was assessed by two GPs with research experience, with no reference made to psychometric standards (instrument construction and measurement procedures) necessary for group comparisons. Test-retest information regarding the reliability of the individual questionnaires was also not provided.[93] Patient satisfaction related to communication, attitude, provision of information and overall satisfaction, was scored on a Likert-scale 0–10, but showed no statistically significant differences in any component measure, with overall satisfaction of the NP group (n=683) mean 8.19 (1.18) versus GP group (n=609) 8.20 (1.26), p = 0.83. Only in a sub-group of patients who reported at least one chronic disease (n = 583), were statistically significant differences found between groups: NP mean 8.35 (SD 1.07) versus GP mean 8.11 (SD 1.32), p = 0.02.[67] Although this significant difference is relatively small, such that it may not be meaningful in practical terms, in the context of chronic disease, it is also possible that this small difference may actually contain clinical significance, in terms of the importance in everyday life over the long term, for chronic disease clients / others with whom these clients interact.[94] Finally, patients with incontinence evaluated patient satisfaction with services using a questionnaire that asked a single open-ended, exploratory question, with no indication of reliability / validity properties related to the conversion of patients' descriptive answers into quantitative results compared between groups**.** Differences in patient satisfaction outcomes for patients with incontinence were: at three months, NP 52% (1294/2498) versus usual care 45% (276/618), 7% difference (95% CI 3-12%), p = 0.001; and at six months NP 64% (1428/2236) versus usual care 53% (289/546), 11% difference (95% CI 6-16%), p < 0.001.[60] At the long term six year follow up, there were no significant differences between-groups in patient satisfaction: NP 55% (1152/2109) versus usual care 52% (306/591), 3% difference (95% CI -2-7%), p = 0.2[81] [Appendices I-9 and J].

4.6.5 'Other' Endpoint-Outcomes

Significant improvements were found in four out of seven trials and one post hoc analysis that measured "other" outcomes not classified by previous categories: maternal / infant health,[69] knowledge,[70] quality of clinical documentation,[62] and psychosocial self-efficacy[7] (patient's belief system / confidence to carry out the behaviour necessary to reach a desired goal) [Appendix I-10]. A wellness-based trial (inclusion criteria of good health at baseline), measured endpoints of maternal / infant health: perceived maternal health, perceived maternal stress, social support, and infant health.[69] Seventy out of 139 newly

discharged, first time low-income mothers in good health postpartum with healthy full-term infants, received intervention that resulted in significantly lower perceived maternal stress (total perceived stress scale scores range 0 - 40 with higher scores indicating higher perceived stress; scores between 14-26 indicate moderate stress): NP mean 14.71 (SD 3.95) versus usual care mean 24.64 (SD 4.61), $p < 0.0001$.[69] Greater perceived maternal health was also significantly improved for intervention participants: NP mean 18.61(SD 1.74) versus usual care mean 17.20 (SD 2.69), $p < 0.0004$, although with scores ranging from 10 (average health) – 20 (perfect health), the difference of 1.41 in mean scores within this range may not be clinically significant. Intervention mothers' perceptions of increased social support, and intervention infants' healthier weight gain with fewer emergency room visits, were non-significant[69] [Table 5; Appendix I-10].

The only other wellness-based trial of this review included women aged 18 to 48 of child-bearing age, with NP (n =51) and usual care (n = 53) groups in presumably good health at baseline, and not yet exposed to any formal nursing class lectures about sexually transmitted infections. Knowledge and perceived risk of sexually transmitted infection in female college students were measured following an educational NP intervention.[70] Significant differences were found in both endpoints of 'knowledge' ($p < 0.0001$) and perceived risk of sexually transmitted infection ($p < 0.0001$)[70] [Table 5]. Disease-specific knowledge was measured in rheumatoid arthritis outpatients following NP and Junior Hospital Doctor care, but only non-significant differences were detected in this endpoint on study completion at 48 weeks.[55] Additional "other" endpoints included 'quality of clinical documentation,' measured in a RS trial of minor injury emergency department (ED) patients, where the aim of the trial was to test methods and tools that could easily be used to evaluate the quality of emergency NP-led care in different EDs.[62] Using a 'Documentation Audit Tool' developed for this study (double blind peer-reviewed), NPs were reported to have written notes of higher quality (94/186 notes) than senior house officers (92/186 notes for SHOs). Scored out of 30 points, comparisons of documentation quality were ENP 28.0/30 versus SHO 26.6/30, $p < 0.001$[62] [Appendices I-10 and J].

Self-efficacy (patients' belief system for effecting change) was measured in a web-based pilot trial of type one diabetes patients,[7] in a pilot trial of older adults transitioning home from hospital,[65] and in a post hoc analysis of cardiovascular disease (CVD) patients attending a risk factor management clinic.[75] A significant difference was found between type one diabetes patients receiving usual care and patients receiving intervention, in terms of self-efficacy with blood glucose management, measured by the Diabetes Empowerment Scale

(NP mean + 0.14 (SD 0.62) versus usual care mean - 0.16 (SD 0.62), effect size of 0.30 (95% CI 0.01 to 0.59), p = 0.044).[7] In contrast, no significant differences in self-efficacy were observed in the pilot trial that evaluated older adult outpatients transitioning home from hospital, following its intervention of up to three home visits and two telephone calls from an NP;[65] nor in the post hoc analysis of an NP intervention providing risk factor management for CVD outpatients.[75] Finally, a RS trial comparing pediatric care provided by a NP to that provided by a dermatologist, detected no significant between-groups differences in 'family impact' related to childhood eczema at baseline, 4, 8, or 12 months. However, given the nature of a RS design, these non-significant differences actually represent positive results between care provided by a NP and care provided by a specialist physician[59] [Appendices I-10 and J].

4.6.6 Meta-Analysis

Reporting of all quantitative patient outcome data from this systematic review's results includes a meta-analysis of NP impact on patient outcomes from homogenous RCTs. Although no combinations of similar study populations, disease states, outcomes, study durations and settings were found among RS trials, similarity of outcomes in similar populations, disease states, study durations and practice settings, were found in two combinations of two IPT trials: a set of two cardiac surgery outpatient RCTs of five to six weeks duration, measuring symptom severity, resource utilization, quality of life and patient satisfaction;[46,48] and a set of two one-year RCTs of cardiovascular disease (CVD) outpatients, measuring blood lipid levels according to treatment goals, and drug utilization.[44,47] However, the latter set of RCTs evaluating blood lipids contained some heterogeneity in their study populations: where one trial was comprised exclusively of coronary heart disease patients,[44] the other trial was comprised of patients with one (or more) of four different CVDs: peripheral arterial disease, abdominal aortic aneurysm, cerebrovascular disease, and coronary heart disease.[47] The former set of cardiac surgery outpatient RCTs was clearly homogenous for further analysis of pooled quantitative data. Non-significant results for all endpoints indicated statistical uncertainty in intervention effect, but not an absence of effect.[37,87]

Of the four sets of similar outcomes for cardiac surgery outpatients, resource utilization data regarding hospital readmission comprised count data most clearly matched (i.e. in terms of emergency room (ER) visits, one study measured 'at least 1 visit to the ER'[46] while the other study simply measured 'total ER visits').[48] Remaining endpoint-outcomes in this pair of studies contained differences including different measurement tools (e.g. different symptom severity instruments), different reporting of data (e.g. no individual data shown for

statistically significant patient satisfaction outcomes in the study by Sawatsky and colleagues[48]), or in the case of global / overall quality of life outcomes, results were of a generic nature that authors of the SF-36 instrument explain are not designed or intended to serve as substitutes for traditional measures of clinical endpoints. Rather, generic measures reflect the combined effects of primary and comorbid conditions while disease-specific measures reflect mainly the primary disease; as such, generic and disease-specific outcomes are best reported in conjunction with each other.[93] As a result, meta-analysis on the practical outcome of unexpected hospital readmission follows, to provide meta-data as required in the transparent reporting of a systematic review, and in particular, according to the protocol of this systematic review.

Equipoise is demonstrated by transparently reporting pooled data from trials found to be homogenous, versus incompletely reporting data to a partial degree, without computation of summary effect in trials found to be homogenous. Particularly in a review designed to capture all quantitative patient outcome data from all settings, transparency is upheld by providing quantitative analysis that is complete. Given the purpose of this systematic review, to "systematically describe the literature pertaining to the nature and impact of NP interventions in health care settings" (section 1.2), obligation rests on provision of data analysis in full. The statement of problem for this thesis (section 1.1) articulates that "independent studies examining the effect of NPs are widely available but an aggregate analysis of these health care providers had never been performed. The systematic assessment of quality, consistency, effectiveness, and scope of this review allows for a comprehensive understanding of the current state of knowledge (including information gaps) about NPs with respect to health care delivery." Indeed, among many reasons noted by Borenstein, Hedges, Higgins and Rothstein for conducting meta-analysis, one reason rests in the logic of trying to understand an entire body of evidence through meaningful synthesis of results that have been gathered systematically, as opposed to understanding studies individually in isolation,[37] without consideration paid to the body of evidence as a whole. Reasons for conducting meta-analyses thus lie beyond the simple reporting of summary effect data, and also include the insight gained by the analysis in terms of designing future research. Certainly this meta-analysis clearly identifies areas where evidence is lacking. That is, the limitations of this systematic review's small-scale meta-analysis, clearly indicate that a greater number of RCTs with larger sample sizes, testing similar interventions in similar circumstances, are necessary to allow for more useful meta-analyses in the future. The level of analysis that this meta-

analysis provides, brings a new perspective for future designs of prospective randomized research testing the effect of the NP.

The larger understanding of this review's entire body of evidence that is gained by the dimension of meta-analysis, also includes understanding the limitations of the technique of meta-analysis itself. Limitations of meta-analysis are similar to those inherent to a systematic review and include: 1) publication bias, referring to the publication or non-publication of research findings depending on the nature and direction of the results;[15] 2) limited availability of methodologically rigorous, high quality (low risk of bias) studies; and 3) non-biased reporting and analysis of all data. However, analysis of funnel plot asymmetry to test for publication bias is not relevant to this meta-analysis of only two studies, since a minimum of 10 studies are required for sufficient capacity to detect bias.[15,39]

Table 6 Similar parameters of resource utilization by cardiac surgery outpatients

Author, Year RCT Design (RS ^ or IPT ^^)	Study Population (Similar Disease State)	Study Duration	Control	Intervention	Outcome	Comment
Tranmer 2004 [46] IPT ^^	200 postoperative cardiac surgery outpatients discharged from first cardiac surgery	Five week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge	*Control* = Usual Care (UC) including education booklet, home-care follow-up as necessary, and NP contact information, with instruction to call with questions or concerns (n= 98)	*Intervention* = Usual Care (UC) + NP initiated phone contacts for patients in 1st 5 weeks following hospital discharge (n= 102)	<u>Total hospital readmissions at 5 weeks post-discharge</u> NP + UC 9 UC 8 p = 0.85	Resource use was tracked through patient self-report
Sawatsky 2013 [48] IPT ^^	204 postoperative cardiac surgery outpatients following first time coronary artery bypass graft (CABG) surgery	Six week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge. Patients with significant issues/concerns were seen at an NP Follow-up (NPFU) Clinic	*Control* = Usual Care (UC) including advice to make primary care provider appointment within 1 week; return visit to cardiac surgeon was scheduled for all patients at 6 weeks (n=107)	*Intervention* = Usual Care (UC) + NP phone contact at 2-3 days post-discharge for 6 weeks, with recommendations to follow-up with primary care provider, cardiac surgeon, receive additional phone contact from NP, go to NPFU clinic, or to local ED (n= 97)	<u>Total hospital readmissions at 6 weeks post-discharge</u> NP + UC 15 UC 19 No p values reported	Resource use self-reported, at the 2 and 6-week post-discharge interviews

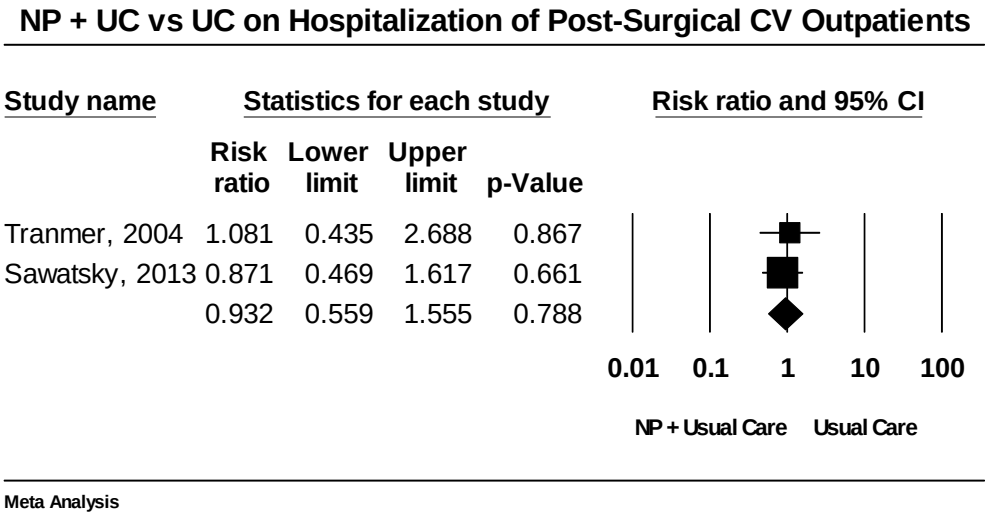
^ Role Substitution (RS) ^^ Interprofessional Team (IPT)

The proportion of hospital readmissions was compared between the intervention and control groups of two homogenous IPT trials.[46,48] Intervention effect data for both trials of cardiac surgery outpatients, as well as the pooled summary effect is displayed below.

	Study name	NP + UC Hospitalization	NP + UC Total N	UC Hospitalization	UC Total N	Risk ratio	Log risk ratio	Std Err	Variance
1	Tranmer, 2004	9	102	8	98	1.081	0.078	0.465	0.216
2	Sawatsky, 2013	15	97	19	107	0.871	-0.138	0.316	0.100

Model	Study name	Statistics for each study				Risk ratio and 95% CI
		Risk ratio	Lower limit	Upper limit	p-Value	0.01 0.10 1.00 10.00 100.00
	Tranmer,	1.081	0.435	2.688	0.867	
	Sawatsky,	0.871	0.469	1.617	0.661	
Random		0.932	0.559	1.555	0.788	

Heterogeneity				Tau-squared			
Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
0.148	1	0.701	0.000	0.000	0.223	0.050	0.000



The intervention effect on hospitalization in the Tranmer trial is a risk ratio is 1.081, and in the Sawatsky trial, the intervention effect is a risk ratio is 0.871. Below the null value of 1.000 (no difference between groups), the risk ratio of 0.871 means that the risk of becoming hospitalized in Sawatsky's intervention group is approximately 12.9% lower than the risk of becoming hospitalized in Sawatsky's usual care group (12.9% less than a risk ratio of 1.0). Above the null value of 1.000, the risk ratio of 1.081 means that the risk of becoming hospitalized in Tranmer's intervention group is approximately 8.1% higher than the risk of becoming hospitalized in Tranmer's usual care group. The greater degree of sampling error in the Tranmer trial is shown by the wider confidence interval; the true intervention effect could be a risk ratio anywhere within the range defined by the confidence interval's lower limit of 0.435 and upper limit of 2.688. Since this interval includes the null value of 1.000, the effect is statistically non-significant, with a p-value of 0.867. In the Sawatsky trial, the confidence interval, although more narrow, providing a more precise estimate (less sampling error), also crosses the null value of 1, with a lower limit of 0.469 and an upper limit of 1.617. Again, since this range includes 1.000, the intervention effect is statistically non-significant, with a p-value of 0.661. However, the superior precision of Sawatsky's effect estimation shown by Sawatsky's more narrow confidence interval, is reflected in the larger solid square displayed in the forest plot, indicating a greater weight assigned to this more precise RCT, using the random effects model.[37]

Although there is no statistical certainty upon which to draw conclusions (all effect sizes are non-significant), this uncertainty in intervention effect on the patient outcome of hospital readmission does not equate to an absence of effect.[87,88] Given that the contribution made to the totality of evidence in a systematic review by studies with statistically non-significant results is as important as the contribution made by studies with statistically significant results, this lack of statistical certainty does not provide basis for exclusion of the effect data from the review's body of evidence.[15] Rather, the opposite is the case. To maintain the scientific integrity of the systematic nature of this review (no reporting bias), the mean summary effect was computed. Using the random effects model, which gives random effects weights to both RCTs for computation, synthesis of the mean summary effect of the two RCTs resulted in a summary risk ratio of 0.932, with a confidence interval of 0.559 to 1.555, and a non-significant p-value of 0.788. This result indicates a 7% lower risk of hospitalization for patients in the intervention group compared to control, although this lower risk is statistically non-significant since the 95% confidence interval contains the null value of 1.000. With reasonable certainty, a 95% level of confidence, the mean summary risk ratio for

this sample of two studies falls somewhere in the range of 0.559 to 1.555, and is statistically non-significant with a p-value of 0.788. The null hypothesis therefore cannot be rejected since the true risk ratio for this sample of two RCTs may be 1.000 (within the range of 0.559 to 1.555). As a result, statistical uncertainty remains regarding the effect of the NP intervention on hospitalization in these two trials, in terms of the NP intervention effect being more or less effective than control in preventing hospitalization.

A small amount of dispersion in the observed effect size is displayed in the forest plot, with risk ratios equalling 0.871 and 1.081. Some of the observed dispersion may be due to differences in the true effects, and some of the dispersion may be due to random sampling error. The Q value (sensitive to the *ratio* of the observed variation to random sampling error),[37] of 0.148 is less than the degrees of freedom (an approximation of sample sizes; a different value for different statistical tests),[77] which means that the amount of dispersion seen in the observed effects displayed in the forest plot, is less than we would expect based purely on the random sampling error, providing no evidence that the true effects actually do vary. Thus, there is no evidence of heterogeneity, accompanied by a non-significant p-value of 0.701. It follows then that I^2, the proportion of dispersion that is probably due to true effects rather than random sampling error[37] is 0.000%, and the estimate of the variance in the true effect sizes between studies, represented by the population value Tau^2 statistic (used to assign weights under the random effects model),[37] is 0.000%.

5.0 Discussion

A systematic review was performed to identify randomised controlled trials (RCTs) testing the effectiveness of NP interventions on quantitative patient outcomes, in order to systematically describe the current state of evidence (nature and impact) in all health care settings, and also to identify areas where evidence is lacking. Of the 29 RCTs identified, the majority focused on NP interventions targeting patients with chronic diseases. These interventions were typically examined on ambulatory patients using an interprofessional (IPT) trial design. The contexts in which the NP role was implemented in these 29 studies were vastly different, across all settings and all levels of prevention. Consequently, the nature of this systematic review's results lend themselves more toward a formative evaluation, providing potential guidance toward health services improvements, than a summative evaluation, although neither of these formal processes were within the realms of this systematic review's protocol.[95] However, the current body of high quality (low risk of bias) studies with the highest internal validity (RCTs) offers a platform of evidence that has been organized, synthesized and summarized in a clear and comprehensive fashion within the rigorous methodology of a systematic review.

Main Findings and Limitations

Out of 89 classes of endpoint-outcomes listed in 10 tables [Appendix I], results for 43 patient outcome classes (43/89; 48%) were statistically significant [Table 4], associated with 26/29 (90%) different RCT interventions. This is a conservative measure of the total number of significant outcomes in this review, meaning that the proportion of total classes [Appendix I] to classes with significant outcomes [Table 4] reflects outcome classes as opposed to individual patient outcomes themselves. For example, 'cardiovascular risk factors' noted as one class in Table 4, and listed as a statistically significant class in Appendix I-2, contains four significant differences in patient LDL-cholesterol, total cholesterol, systolic blood pressure, and body mass index.[47] Statistically significant effect sizes ranged from between-groups differences of 40% ($p < 0.001$) in chronic heart failure outpatients that were initiated or up-titrated on beta-blocker medication, with 33% ($p < 0.001$) more chronic heart failure patients from the NP intervention group reaching target guideline doses of beta-blockers;[45] to a mean change in the Diabetes Empowerment Scale score of 0.30 (95% CI 0.01 to 0.59, $p = 0.044$) in the evaluation of type one diabetes patients' self-efficacy.[7] Three RCTs did not detect any statistically significant differences between groups in patient outcomes: 1) a RS trial measuring the effect of NP care on outcomes for internal medicine patients, compared to usual care by house-staff,[71] 2) an IPT trial measuring the effect of a mobile NP service on

recovery of 33 hip fracture surgery patients post-hospital discharge (10 patients lost to follow-up),[64] and 3) an IPT trial measuring the effect of a NP phone intervention on preventing glycemic relapse in type two diabetes patients who had recently achieved glycemic control.[51] Interventions associated with statistically significant outcomes were often associated with clinical significance for the patient, in terms of the minimal clinically important difference (MCID, the smallest change in a patient outcome that a patient would identify as important for potential change in patient management[15]) but not consistently. For example the exploratory pilot trial that tested a patient-initiated system of scheduling treatment for symptoms of chronic obstructive pulmonary disease (COPD), found statistically and clinically significant differences in the symptom domain of the 'Clinical COPD Questionnaire' (CCQ, specific to COPD); borderline significant differences in the symptom domain of St. George's Respiratory Questionnaire (SGRQ is less specific to COPD than the CCQ; the SGRQ is designed to measure impact on overall health and perceived well-being in patients with respiratory diseases in general), reaching the MCID for the SGRQ; and differences in certain SF-36 domains (non-disease-specific / global quality of life measure) that reached the MCID, yet were too variable overall to be considered significant (bodily pain, role emotional, and mental health).[50] Further, it was not uncommon that a study contained statistically significant patient outcomes in certain endpoint categories but not in others, resulting in an overall sense of clinical significance to the study itself. For example, the study intervention of Web-based NP case management for Type 1 Diabetes patients did not have a statistically significant impact on physiologic markers [Appendix I-2], but was associated with a beneficial, statistically significant effect on self-efficacy ('other' outcome), related to the patient's self-management of their chronic illness [Appendix I-10].[7]

Specific domains of activity indicated that diagnostically, NPs were rarely used to full scope, with open diagnosis occurring only in 1/29 RCTs, limited diagnosis in 9/29 RCTs, and diagnosis of disease status in 17/29 RCTs. It followed that open prescribing occurred in only one out of 20 RCTs, with prescribing activity in the remaining 19 RCTs of a limited nature. Clinical procedures were the least commonly performed activity although this was not surprising given that only three out of 29 RCTs were set in acute care. 'Strategies for behaviour change' relative to education activity were found prevalent in the outpatient environment at 56% of all activity in this domain, addressing the higher proportion of chronic disease for outpatients [upper segment Table 3]. Conversely, the activity of education which is classic prevention, was predominantly found in the primary health care environment further upstream at 62.5% of all activity in this domain, in the management of a higher

proportion of primary and secondary prevention trials with less chronic disease [upper segment Table 3]. In the most urgent environment of acute care, no evidence of 'strategies for behaviour change' was found, although education was always inferred in the intervention (instructions during hospital stay / discharge teaching). Care coordination, an offsite activity, naturally did not occur in the acute care environment, and was found in 50% of all outpatient trials and 25% of all primary health care trials [upper segment Table 3].

In terms of the mode of NP implementation, naturally, care coordination occurred more-so in IPT trials (9/20; 45%) relative to RS trials (2/9; 22%) [lower segment Table 3]. Further, IPT trials contained the higher proportion of non-acute trials set in less urgent environments than RS trials, with likely, more availability of time in which to exercise strategies for behaviour change. Strategies ranged from practitioner-to-patient in RS trials,[56] to team-to-family in IPT trials where the patient included family.[64] In contrast, the traditional activities of diagnosis, prescribing and clinical procedures were performed less often in the IPT mode than in the RS mode, while strategies for behaviour change and care coordination may be considered to be more proactive activities employed by collaborative team modes of care [lower segment Table 3].

The most critical life-threatening endpoint-outcomes were categorized first, notably the smallest category of endpoint-outcomes. This review found the largest category of endpoints to be 'surrogate measures of disease' indicating an emphasis in NP intervention research less directly on the immediate life-threatening issues of individual patients, and more-so on the 'systems-threatening issues' of long term tertiary prevention manifest in the permanent aspects of chronic disease. Resource utilization / cost endpoints were measured in all settings and found results ranging from significant reductions in healthcare charges for low-income maternal / infant patients[69] [Table 4; Appendix I-7] to non-significant reductions in hospital / ancillary costs for internal medicine patients[71] [Appendix I-5]. However, the quality of these estimates was often limited related to the component of self-reported data (e.g. cost diaries) that was not able to be consistently cross-checked with formal medical records. One RCT reported higher utilization of emergency care for intervention patients post-operative to suspected ovarian cancer, with control patients visiting primary care significantly more frequently[79] [Table 4; Appendix I-6]. Additional significant results were found in endpoints of patient satisfaction, reported in seven out of eight RCTs [Table 4; Appendix I-9] and in "other" endpoints, reported in four out of eight RCTs [Table 4; Appendix I-10], from all settings in both cases. Only one RCT found statistically significant

improvement in overall / global quality of life, for women discharged home post-operative to suspected ovarian cancer[52] [Table 4; Appendix I-8].

Twenty-six RCTs found a total of 43 classes of statistically significant endpoint-outcomes [Table 4]. Where nine out of these 26 RCTs found statistically significant results in resource / cost outcomes, five of these trials were RS and four were IPT trials. Significant resource / cost outcomes were thus, relatively evenly distributed between the RS and IPT design. However, on consideration of all statistically significant endpoint-outcomes, 17/43 (40%) classes of statistically significant results were derived from 8/9 (89%) of the RS trials, that overall, comprise only 31% (9/29) of the review's RCTs. Almost half of the review's statistically significant outcome classes were derived from the less prevalent RS mode of implementation [Table 4]. This is surprising in light of our hypotheses that anticipated the opposite. It was anticipated that IPT studies would have produced the highest number of statistically significant differences based on the IPT design of the "+1" team member, and that RS results would generally be at best, equivalent between intervention and control groups.

Based on these findings, it appears that the greatest clarity in learning of differences that distinguish the NP role from that of other health care providers (within specific contexts), may be derived from RCTs of the RS design. This is not to say that focus of potential future change initiatives in practice, be based primarily / necessarily on direct translation of actual RS study designs, but rather that the most informative research may focus on RS designs, to inform practice that inevitably necessitates IPT frameworks. Interestingly, in both cases of RS / IPT trials, a common approach found in study design was with regards to 'utilization of the NP role within a team framework.' In other words, study authors would commonly explore the question "how can the NP be utilized in a way that maximizes or "potentiates" the productivity and expertise of the complementary provider(s)?" This question was explored regardless of whether the trial was RS or IPT. For example, strategic use of the NP was discussed by Dierick van Daele following the economic evaluation of their RS trial on common complaints in primary health care.[27]Authors maintained that when common conditions are extracted from the repertoire of GP consultations, the GP role may then be allowed to expand, to focus on patients with more complex diagnoses or multi-morbidity, and to coordinate with other professionals, reflecting teamwork strategies on the part of GPs, teamwork strategies that stem from the discussion of a RS trial. While healthcare system redesign requires the system to take a long-term perspective, and may be difficult to achieve in practice, mutual goals more easily and appropriately become the focus for change when

goals are set within the framework of IPT that includes the patient at the center of both the team and the larger frame.

An example of an IPT trial that explored the question "how can the NP be utilized in a way that maximizes or "potentiates" the productivity and expertise of the complementary provider(s)?" was found in a pilot RCT of chronic heart failure (CHF) patients' adherence to beta-blocker medication.[45] The NP facilitator intervention was designed to maximize specific aspects of the NP role, with study authors stating "We used a NP in our study because physical examinations play an important role in patient selection and monitoring during beta-blocker initiation" (p. 2803).[45] The NP was supervised by two cardiologists until the CHF patient reached the target or maximum tolerated beta-blocker dose, at which time, the patient was returned to their primary care provider for all additional care. This exploratory pilot RCT contains the review's largest effect, a 33% difference between the NP facilitator intervention and the control group in the number of CHF patients on target doses of beta-blockers at study end (median follow-up, 12 months, $p < 0.001$).[45] However, past ensuring that application of the NP role maximally aligns within the context and goal of the patients' needs, the NP role, as with any other advanced healthcare professional is complex, so that it may be counter-productive to speculate on a single dimension of the NP role's "dose" affecting positive impact in a clear way, without oversimplifying the role itself, and the patients' needs in context.

Limitations of the body of evidence in this review include an absence of power analysis to determine appropriate sample size in the majority of RCTs (16/29; 55%), limiting the rigor within which most patient outcomes were assessed. A limitation of this review's results framework includes the potential overlap between quality of life endpoint categories, with disease-specific quality of life endpoints classified within the category of 'surrogate measures of disease,' and 'non-disease-specific, global quality of life' endpoints classified within the category of 'quality of life / patient satisfaction.' As the authors of the SF-36 tool explain, global / generic quality of life measures are universally valued in health status assessment, but are not age, disease, condition, or treatment specific. As such, they are not designed or intended to serve as substitutes for traditional clinical endpoints measures.[93] Where ideally, the impact of disease on health status is evaluated using both generic and disease-specific measurement tools in parallel, then accordingly, ideally, these two types of quality of life measures would have also been reported in parallel in this review. Analysis of patient-satisfaction outcomes involved little common ground for between-study comparisons, based on the fact that different tools were used in each study that measured patient

satisfaction. Unique to the category of 'other' endpoint-outcomes were both sets of wellness-based outcomes,[69,70] and all measures of self-efficacy.[7,65,75]

Limitations of this review overall, include 1) the limited number of homogenous RCTs that could be appropriately combined for analysis of quantitative data, and 2) the temporal bias of the literature, including RCTs published only since the year 2000, with the intention of maintaining relevance to present healthcare system dynamics and to the present nature of the NP role itself, according to the rationale that both the healthcare system and the NP role itself, have changed significantly since 1973. Further, categorization of NP practice into domains for the purpose of objective one, facilitated reporting of the research on exclusively the NP role in randomised trials, but does not exemplify the complete nature of the NP role in practice. Results of the present systematic review and meta-analysis provide insight into the nature and impact of NP interventions tested in RCTs, through various combinations of domain activity. Execution of a single domain of education / strategies for behaviour change activity, in the absence of any other activity in two RCTs' tests of NP effectiveness,[68,70] constitute limitations in the aggregate body of RCT data, given the multi-faceted nature of the NP role.

Context of Other Evidence

There are no previous systematic reviews of randomised controlled trials testing the effectiveness of NP interventions in all settings. However, two landmark RCTs[29,96] that were designed upon the formation of an educational program for NPs, jointly sponsored by the School of Nursing and the Faculty of Medicine at McMaster University in 1971, provide contrasting perspective to the eight primary health care RCTs of this review [Appendix K]. Designed at a time of patient saturation in family practice clinics (no new patients accepted) and nurse surplus in Ontario, Canada, these two RCTs evaluated the NP role at the time of its formal inception into the healthcare system in 1973.[5] Findings of this review indicate that randomised trial research on the NP role has since expanded from the original primary health care setting into the outpatient and acute care settings, six times more so in the outpatient than the acute care setting (18 outpatient RCTs: 3 acute care RCTs), with no randomised NP research to date set exclusively in long term care. The only two RCTs designed to test interventions in older adult populations were pilot trials.[64,65]

The original non-inferiority trial that ran from July 01, 1971 to July 01, 1972 was designed by Dr. W. Spitzer, a Canadian physician with background in primary care practice and epidemiology.[29] This RCT tested the effects of the newly defined NP role compared to GPs, on patient health status in primary care, with the family as the unit of random allocation

[Appendix K]. In this non-inferiority trial, the greatest degree of 'worse functional outcomes' tolerated from NP care before declared 'inferior' was set at '5% worse.' Study results indicated that the probability of NP patients being 'worse-off by 5% or more' was 0.008, or a likelihood of one chance out of 125 chances.[97] Results showed the NP to be clinically safe, effective and cost-effective from a societal perspective, based on patient outcomes and a 22% net increase in families accepted into primary care practice during the one year trial period. Families receiving primary health care continued to increase so that at one year follow-up, an additional increase of 19% plateaued at 41% more families (2256 families receiving care by June 30, 1973) compared to the baseline value of 1598 families receiving care on July 01, 1971.[29] However, this societal benefit was not realized economically by the physicians' primary care practice, due to restricted reimbursement for NP services. At the time of the trial, Ontario regulations did not permit billing for unsupervised NP services previously provided by GPs, where GP services were reimbursed by government health insurance according to the Ontario medical association's fee schedule.[29] A second RCT accompanied the original non-inferiority trial, in order to test the effects of NPs upon the professionals themselves, in a team mode, with NPs functioning as co-practitioners alongside GPs in intervention practices, compared to usual care provided by GPs and RNs in control practices[96] [Appendix K]. Despite positive results in the professional outcomes of job satisfaction, views of each other's role, and impact on clinical activities, and despite positive financial results found in the economic evaluation of this same trial (net earnings of the experimental practices increased in three practices, remained unchanged in two, and decreased in one practice; compared to no change in four control practices, an increase in one, and a decrease in another control practice, even without reimbursement for unsupervised NP services),[98] no regulatory changes were made to govern reimbursement of NP services at that time. As noted in 1973, whether or not patients and practitioners were both positively affected by the integration of NP services, replication of new modes of care would not be of benefit to the public without regulatory change that is viable to all professionals according to the primary interests of the public their professional services are intended to serve.[98]

Almost 50 years ago, during the time of family practice saturation in southern Ontario, the element in question was how to meet the demand for health services in primary care. By now, the element in question relates instead to the health system in its entirety, in terms of health services delivery to the public in all settings, not only in primary care, but with NP services as one component, currently found heavily imbalanced downstream according to the results of this systematic review. In fact, the proportion of 9/12 RCTs (75%)

that were not set in acute care but nonetheless, reported acute care utilization, suggests a significant reliance on acute care services by patients from the outpatient and primary health care settings. Utilization of NP services predominantly downstream in the outpatient (18 RCTs) and acute care (3 RCTs) settings relative to primary health care (8 RCTs), compound financial challenges to the system in these downstream settings that are also generally, more expensive. In contrast, wellness-based outcomes such as the maternal / infant health [69] and knowledge,[70] have the potential to compound economically in the other direction, through practical benefits inherent to primary prevention. Negotiation of cost components associated with new models of care, recognized by the original landmark trials as the fulcrum point for further replication of NP integration or not,[98] was evaluated approximately midway between 1973 to present, in the 1996 *Recommendations of the Panel on Cost-Effectiveness in Health and Medicine.*[92]

The Panel on Cost-Effectiveness in Health and Medicine examined costs associated with health interventions, and recognized the societal perspective that encompasses prevention initiatives upstream, in addition to the more commonly considered downstream costs. Major categories of resource / costs identified by the Panel include costs of health care services; costs of patient time expended for the intervention; costs associated with caregiving (paid or unpaid); other costs associated with illness such as childcare and travel expense; economic costs borne by employers, other employees, and the rest of society, including 'friction costs' associated with absenteeism and employee turnover; and costs associated with non-health impacts of the intervention, for example, on the educational system, the criminal justice system, or the environment.[92] In terms of this review, while RCTs commonly provide individual patient data for cost-effectiveness analyses, a single RCT is unable to compare all available options, provide evidence on all relevant interventions, or be conducted over a long enough time to capture differences in economic outcomes (or even measure those outcomes), thus necessitating decision analytical modelling, that compares the expected costs and consequences of decision options by synthesizing information from multiple sources.[99] However, in this systematic review, related to the careful attention paid to similarity of studies for meta-analysis, correspondingly, it was verified that no combinations of economic evaluations were eligible for comparability of treatment patterns across jurisdictions.[100]

Yet statistically significant resource / cost outcomes were found in nine out of 14 RCTs that measured these endpoints, in all settings [Table 4]. Cost endpoints in particular, were measured again, in only nine[27,50,60,66,69,71,78,83,86] of the 14 studies measuring resource / cost endpoints. Four of the nine studies measuring cost, found statistically significant

reductions for 1) outpatient care of pediatric eczema patients and their families,[78] 2) primary health care in patients with 'common complaints,'[27] 3) NSAID costs in patients with chronic musculoskeletal pain,[66] and 4) costs for postpartum care of maternal / infant patients.[69] Societal costs were acknowledged in three of these four trials,[27,66,78] although two of these cost analyses were conducted post hoc to the original trial.[27,78] Methods of cost analysis used in this review included cost minimization evaluation in two RS studies,[27,86] and cost-effectiveness analyses (CEAs) in four studies (one RS study[78] and three IPT studies[60,66,83]), with three RCTs not referring to a formal method of cost analysis: an IPT pilot trial reported "total costs of healthcare resource use per COPD outpatient;"[50] a RS trial acknowledged its intention was not to conduct a comprehensive cost analysis but rather, to only report a comparison between groups on "total healthcare charges;"[69] and lastly, a RS trial of internal medicine inpatients assessed costs of care to principally reflect the use of discretionary hospital resources (e.g. bed days, diagnostic tests), for between-group comparison, without any analysis of the salary differential between NP and house-staff , nor the costs of the medical director, or of providing off-hours coverage by residents.[71] Three studies found that statistically significantly reduced cost was largely due to the salary differential of professionals within the trial: NPs and GPs in primary health care;[27] NPs and dermatologists in outpatient care;[78] and NPs and pediatricians in primary health care.[69]

Interestingly, where acute care utilization was the most prevalent type of resource utilization reported in this review, measured in 12 out of 14 RCTs that measured resource / cost endpoints, only one acute care RCT found a significant result in its endpoint of wait times for emergency department patients, without any associated cost evaluation.[62] The most commonly found significant differences in resource utilization were reductions in primary health care (PHC) visits, measured in four outpatient studies regarding: older adults transitioning home post-hospital discharge,[65] women discharged home post-operative to suspected ovarian cancer,[79] pediatric patients with eczema and their families,[78] and COPD patients that utilized an on-demand, patient-initiated system of outpatient scheduling.[50] This latter 'on-demand' intervention of patient-initiated scheduling, tested in a pilot trial of COPD outpatients, represents a novel pro-active approach to health care that was also observed in the pro-active phone intervention for low-income postpartum mothers and infants.[69] Both RCTs increased access to the NP, with interventions resulting in clinically and statistically significant improvements at lower total costs in both cases. Low-income postpartum families with mothers and infants in good health at baseline, experienced statistically significantly improved maternal health outcomes [Appendix I-10], and statistically significantly reduced

healthcare charges for their infants [Appendix I-7].[69] COPD outpatients were more in control of their symptoms, experiencing significantly less deterioration in their COPD symptoms (Clinical COPD Questionnaire (CCQ) symptom scores reached the minimal clinically important difference, or MCID), while experiencing cost-savings from both the healthcare provider and the healthcare insurance perspective. However, compared to the control group of COPD patients, reductions in total costs for intervention outpatients from both the provider and insurance perspectives, were not statistically significant, although this RCT was a pilot trial not designed for cost analysis.[50]

Indeed, Bauer, an internationally recognized medical economist with 17 years' experience as professor of statistics and research at two medical schools, recognized the necessity of "allowing patients to receive all the clinical and economic benefits of direct access to NPs, where Americans are paying an unnecessarily high price for a system that denies direct access to the cost-effective provider of many basic health services."[20] Novel proactive, collaborative approaches seen in this review through the patient-initiated system of outpatient scheduling[50] as well as in the primary prevention intervention for low-income postpartum families, delivered offsite via phone,[69] provide examples of patient-focussed approaches to proactive healthcare at reduced cost. The primary prevention RCT is also an example of a RS trial whose research evidence ultimately informs practice that utilizes a team framework. That is, evidence from the RS trial (that compared offsite NP care to routine pediatrician care), may inform future practice of collaboration between the NP and the postpartum mother. Bauer also recognized that NPs are leaders in providing home care and care at worksites, two locations where demand is growing faster than the health system's capability to meet challenges.[20] NP interventions contained the component of home care services in six (6/29; 21%) of this review's RCTs: a trial of a newly designed incontinence service delivered by NPs,[60] a trial of a NP-delivered educational package for NSAID reduction in patients with chronic musculoskeletal pain,[66] a trial of psychosocial sessions delivered by a NP for depression in ischemic stroke outpatients,[54] as well as three RCTs that followed patients discharged home from hospital: women with suspected ovarian cancer,[52] hip fracture surgery patients,[64] and older adults discharged home from hospital stays.[65]

Implications for Future Research

New perspectives for future design of prospective randomised research testing the effectiveness of the NP role were noted within the limitations of this review's meta-analysis: a greater number of RCTs with larger sample sizes, testing similar NP interventions in similar circumstances, are necessary to allow for more useful meta-analyses in the future. In terms of

specific RCT design, based on the proportion of significant findings derived from the RS trials of this review, with note taken of the non-inferiority design of the landmark RS trial of 1974 (comparing NP care to GP care with the family as the unit of random allocation), future RCTs may consider application of the non-inferiority RS design. Traditionally, significance testing in randomised between-group studies, has examined the superiority of an experimental treatment to a comparator group. However, research questions that seek to determine whether two treatments are neither clinically nor statistically different, have become increasingly important in light of prevailing system constraints. For example, if a novel intervention claims to be safe, high quality, and potentially less expensive / more accessible, then the research goal may be to show that its effectiveness is not much less if at all, than that of standard treatment in a particular context. Tests of whether novel interventions are at least as effective as established interventions with proven effectiveness, provide answers that traditional superiority designs cannot completely address.[85]

Furthermore, despite common interchange in terminology, non-inferiority trials differ from equivalence trials. Where non-inferiority trials determine whether an intervention is "no worse" than standard treatment, using a one-sided statistical test (non-inferiority margin), equivalence trials determine whether an intervention is either "no better or no worse" than standard treatment, using a two-sided statistical test (equivalence margin). Equivalency designs are less commonly used in therapeutic trials evaluating effectiveness, since the study objective in a therapeutic trial is to show that a new treatment is not inferior to a standard (non-inferiority design), versus showing that the new treatment is neither inferior nor superior to the standard (equivalency design). However, methodological challenges inherent to the design of a non-inferiority trial are considerable since a poor trial design can erroneously suggest a similarity. Challenges include: the choices of an active control treatment (this design cannot be used without a well-established standard treatment), a non-inferiority margin, sample size and statistical analysis.[85] Two trials[27,86] from this review performed cost minimization evaluations (on the knowledge or assumption that competing interventions had the same health effects, comparison was made on cost alone; controversial method, since two interventions are rarely equally effective[91]) post hoc to their RS trials, deemed equivalence trials.[63,67]However, only one of these two trials actually designated a margin of equivalence,[63] within which the intervention may be shown to be neither inferior nor superior to the standard treatment.[85]

Overall, the twenty-nine RCTs (year 2000 – present) of this systematic review provide evidence that may inform utilization of NP services to the extent of its findings,

according to the summary of quantitative data that it provides from all settings studied (no studies were set in long term care). Given the deliberately broad scope of the systematic review's design, NP intervention impact was not expected to be determined in terms of a definitively clear and exact numeric value, but rather NP impact was expected to be largely described as thoroughly as the protocol outlined would be done, with quantitative meta-analysis conducted where possible. Transparent analysis of NP effect included primarily descriptive report of various endpoints unable to be pooled, as well as results from one pair of homogenous IPT trials pooled for quantitative meta-analysis.[37] Results suggest that NP interventions, whether tested in RS or IPT designs, may be effective in primary health care, outpatient care and acute care settings on aspects of virtually all endpoint categories [Table 4], with the exception of clinical outcomes. No statistically significant differences were found in the clinical outcomes of this review, although of the three RCTs that measured clinical endpoints, two were RS trials comparing practitioners in specific contexts,[49,71] and the third was an IPT pilot trial designed less for hypothesis testing than for learning of research feasibility[45] [Appendix I-1]. Only one study out of nine that measured global quality of life detected significant results, derived from mixed effects regression models.[52] However, all nine trials that measured global, overall quality of life, used the medically-oriented SF-36 tool (or smaller derivations) to measure patient outcomes resulting from nursing interventions [Appendix I-8].

The context of all settings in this review, and the evaluation of all quantitative patient outcomes of NP interventions tested in RCTs, may together, provide insight into the design, function, and limitations of the health system as a larger whole. That is, results of this review presented within its system context of all settings, may provide insight into the design and functional challenges of adequate health service provision overall, within a systems-level-context of limitations. For example, while service challenges in primary health care were initially addressed in part by the formal inception of NPs in the early 1970's, present day challenges continue to utilize the capacity of the versatile NP role in addressing still similar challenges, now amplified across the entire system in all settings, limiting the system by this very amplification. Despite the burden healthcare carries in terms of chronic disease management (tertiary prevention), reflected in 17 out of 29 (59%) RCTs of this review, only 41% of the review's RCTs focused on either primary prevention, aiming to prevent disease or injury before it ever occurs;[13] or secondary prevention, aiming to reduce the impact of a disease or injury that has already occurred, to halt or slow its progress.[13] Furthermore, of the 10 RCTs categorized as secondary prevention trials, only one trial focussed its intervention

on obese / overweight patients with the explicit goal of disease prevention.[56] Two out of 29 RCTs (7%) from this review were designed in the context of primary prevention, evaluating NP intervention effects upon the maintenance of good health[69,70] [Table 5; Appendices I-7 and I-10].

Reinforcing this imbalance in the primary-to-secondary-to-tertiary prevention spectrum, is the fact that the single RCT that tested an intervention explicitly for prevention, was also the one and only RCT that focused on the issue of obesity,[56] known to be very significantly and directly linked with many other chronic diseases.[56] This scarcity of RCT evidence testing NP intervention effects on the highly-linked condition of obesity (now considered a chronic disease in itself),[57] is an example of a very significant design challenge for future research. Similarly, despite the expanding demographics of aging populations, there was not one RCT found in this review set exclusively in long term care. The trial that evaluated older adults postoperative to hip fracture examined some of the patients in the long term care environment, but only as one of three non-acute settings in which follow-up took place.[64] Recognition of large and very significant gaps such as these, between research conducted and challenges currently faced in healthcare, statistically and demographically, may serve as a starting point for collaborative solutions management across settings.

Conclusion

Delivery of healthcare services in a world with limited resources and increasing pressure to create evidence-based quality patient outcomes,[16] may require evidence-informed IPTs that most effectively utilize resources, resources that include patients themselves in an integral, central position within healthcare teams in all settings. The high quality (low risk of bias) research findings of this systematic review reveal substantial gaps between activities set in downstream environments relative to the upstream settings requiring development. These gaps point to the design of future research that may illuminate more clearly, necessary new directions in healthcare that are balanced between the up and the downstream, so that health services may be experienced by all members of the public, in all regions, remote and urban. Integration of innovative, pro-active patient-centered initiatives further upstream into the healthcare system may prevent the lifelong management of chronic health challenges that drain both the individual patient, and the system itself in the long term. Key elements of this system include the five principles of the 1984 Canada Health Act: universality, portability, public administration of funds, accessibility, and comprehensiveness. Evaluation of these principles in the face of many complex challenges requires expert opinion, recently supplied by the Honorable Dr. Kevin Lynch, Former Clerk of the Privy Council, in his statement:

"there is *enormous* scope for innovation consistent with the principles of the Canada Health Act" (December 04, 2015).[101] Balancing complex healthcare demands through strategic and innovative application of ever evolving knowledge, together with patients as partners in their own healthcare management, restores the resourcefulness needed to meet complex, systemic challenges throughout all components of the healthcare continuum, both the up and the downstream, over the long term.

Appendix A Relevance Tool

Study Citation (*surname of first author, title, year first full report of study published, publisher, abstract / full article)*
Reviewer Initials: _____

INCLUSION CRITERIA

- ☐ Randomised trial. Randomisation at both 1) individual level & 2) cluster level, only if there are *multiple clusters* (> 15 clusters / group) in both intervention *and* control groups.
- ☐ NP Intervention implemented via either mode of role substitution (RS) or interprofessional team (IPT). All types of NPs will be eligible. Various titles include PHCNP (Primary Health Care NP), ACNP (Acute Care NP), NNP (Neonatal NP), ARNP (Advanced Registered NP), ANP (Advanced NP) etc. Context of program studies will be included if the NP is the "+1" member of the intervention IPT compared to an otherwise identical control IPT, or if the program is delivered exclusively by the NP(s).
- ☐ Primary health care patients, long term care residents, outpatients (not admitted overnight to hospital) / specialized referrals, OR emergency department patients / acute inpatients receive the intervention.
- ☐ Quantitative endpoint must be from the following categories:
  - Death
  - Hospitalization (MI / stroke / life-threatening event)
  - Treatment of a Chronic Disease (surrogate markers of disease may include physiologic markers e.g. blood glucose in diabetes; symptom severity e.g. post-operative symptoms in cardiac surgery outpatients; functional status e.g. peak flow in asthma patients; behaviour/lifestyle change e.g. diet in obese patients)
  - Drug Utilization (i.e., adherence or 'appropriate prescribing')
  - Resource Utilization (consultations, tests / investigations, referrals)
  - Cost
  - Quality of Life and / or Patient Satisfaction
  - Other
- ☐ Publication date of the study 2000 or later.
- ☐ Study published in English.

EXCLUSION CRITERIA
Studies will be excluded if they do not specify "nurse practitioner" (with various descriptive wording noted above possibly preceding the title of NP) as the sole nursing intervention. Examples of other types of non-NP nursing professionals include:

- ☐ Clinical Nurse Specialist
- ☐ Community Health Nurse
- ☐ Public Health Nurse

Must satisfy all 6 inclusion criteria and 3 exclusion criteria

INCLUDE? ☐YES ☐ NO

Appendix B Validity Tool

Risk of Bias Assessment

Domain	**Risk of bias** Yes, Low risk ☐ No, High risk ☐ Unclear ☐	**Support for judgement** from Criteria Table 8.5c (Higgins & Green, 2008, p. 198) according to modifications by Donald et al., 2014, p. 3)	**Location in text** *(page)*
Random sequence generation likely to produce comparable groups *(selection bias)*	☐ ☐ ☐		
Allocation concealment so that group allocation could not be foreseen in advance *(selection bias)*	☐ ☐ ☐		
Appropriate method or source was used to collect objective outcome measures *(detection bias)*	☐ ☐ ☐		
Outcome data complete for objective measures at > or = to 80% of sample & missing data imputed appropriately *(attrition bias)*	☐ ☐ ☐		

Outcome reporting All outcomes described in the methods section were reported in results *(reporting bias)*	☐ ☐ ☐		
Other biases detected in the study may, among others, include: Contamination Bias (e.g. the control group had exposure to the intervention) Measurement Bias (e.g. whether the study used a validated tool / procedure to objectively measure the outcome)	☐ ☐ ☐		
Notes: **Overall Risk of Bias =** Low: 0-1 'at risk' or 'no' judgements Moderate: 2-3 'at risk' or 'no' judgements High: 4-6 'at risk' or 'no' judgements			

Appendix C Data Extraction Form

1. General Information

Citation
Country and Year of Intervention
Purpose
Study Design
Environment for Type of Care (Circle one) → Primary Health Care / Long Term Care / Outpatient (not admitted overnight to hospital) or Specialized Referral Care / Emergency Dept. Care or Acute Inpatient Hospital Care **Specific Description of Practice Environment** **Types of NPs** **Types of IPT members**
Patient population: Inclusion / exclusion criteria for study participation
Baseline Characteristics / Description of final study sample (n) as stated in study

2. Intervention

Mode of NP Implementation (circle one): a) RS b) IPT

Types of NP intervention activities undertaken:
DETAILS:

☐ **Diagnosis**

☐ **Prescribing i)** ordering medications in **acute care**

ii) ordering medications in **primary care, long term care or outpatient**

including the ongoing medication management of **chronic disease patients**

☐ **Clinical Procedures**

☐ **Education & 'Strategies for Behaviour Change'**

☐ **Care Coordination**

Description of Control (or Standard Care)

Comments:

3. Endpoints/ Results

Endpoint #1 ☐ Death ☐ Hospitalization (MI / stroke / life-threatening event) ☐ Treatment of a Chronic Disease (surrogate markers may include improvements in BP for hypertension, blood glucose for diabetes mellitus, etc.) ☐ Resource Utilization (consultations, tests/investigations, referrals) ☐ Drug Utilization (i.e., adherence or 'appropriate prescribing') ☐ Cost ☐ Quality of Life &/or Patient Satisfaction ☐ Other	☐ **Primary Endpoint** ☐ **Secondary Endpoint** **Details as stated in study / Derivation:** **Validity of endpoint:** **Primary Endpoint** **Secondary Endpoint** **Follow-up complete?**	**Results:** **Intervention:** **Control:**

Endpoint #2 ☐ Death ☐ Hospitalization (MI / stroke / life-threatening event) ☐ Treatment of a Chronic Disease (surrogate markers may include improvements in BP for hypertension, blood glucose for diabetes mellitus, etc.) ☐ Resource Utilization (consultations, tests/investigations, referrals) ☐ Drug Utilization (i.e., adherence or 'appropriate prescribing') ☐ Cost ☐ Quality of Life &/or Patient Satisfaction ☐ Other	☐ **Primary Endpoint** ☐ **Secondary Endpoint** **Details as stated in study / Derivation** **Validity of endpoint:** **Primary Endpoint** **Secondary Endpoint** **Follow-up complete?**	**Results:** **Intervention:** **Control:**

Endpoint #3 ☐ Death ☐ Hospitalization (MI / stroke / life-threatening event) ☐ Treatment of a Chronic Disease (surrogate markers may include improvements in BP for hypertension, blood glucose for diabetes mellitus, etc.) ☐ Resource Utilization (consultations, tests/investigations, referrals) ☐ Drug Utilization (i.e., adherence or 'appropriate prescribing') ☐ Cost ☐ Quality of Life &/or Patient Satisfaction ☐ Other	☐ **Primary Endpoint** ☐ **Secondary Endpoint** **Details as stated in study /** **Derivation:** **Validity of endpoint:** **Primary Endpoint** **Secondary Endpoint** **Follow-up complete?**	**Results:** **Intervention:** **Control:**
Statistical methods used & appropriateness		

4. Other

Key conclusions of study authors as stated in study	
References to other relevant studies	
Correspondence required for further study information	
Notes	

Appendix D PRISMA Statement

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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Appendix E PRISMA-P 2015 Checklist

Table 2| **PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol**

Section and topic	Item No	Checklist item
Administrative information		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
Introduction		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
Methods		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

Appendix F Draft Search Strategy in Ovid MEDLINE

Ovid MEDLINE search strategy for the role and impact of Nurse Practitioners in Randomized Controlled Trials

---

1. Randomized controlled trials as Topic/

2. Randomized controlled trial/

3. Random allocation/

4. Double blind method/

5. Single blind method/

6. Clinical trial/

7. exp Clinical Trials as Topic/

8. or/1-7

9. (clinic$ adj trial$1).tw.

10. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.

11. Placebos/

12. Placebo$.tw.

13. Randomly allocated.tw.

14. (allocated adj2 random).tw.

15. or/9-14

16. 8 or 15

17. Case report.tw.

18. Letter/

19. Historical article/

20. Review of reported cases.pt.

21. Review, multicase.pt.

22. or/17-21

23. 16 not 22

24. nurse practitioner.mp. or *Nurse Practitioners/

25. family nurse practitioner.mp. or *Family Nurse Practitioners/

26. pediatric nurse practitioner.mp. or *Pediatric Nurse Practitioners/

27. (nurse adj2 practitioner*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

28. nurse practitioner.ab. /freq=2

29. advanced practice nursing.mp. or *Advanced Practice Nursing/

30. 24 or 25 or 26 or 27 or 28 or 29

31. interprofessional relations.mp. or Interprofessional Relations/

32. Intervention Studies/ or intervention.mp.

33. patient care team.mp. or *Patient Care Team/

34. Interdisciplinary Communication/ or interdisciplinary.mp.

35. nurse role.mp. or Nurse's Role/

36. interprofessional team.mp.

37. role substitution.mp.

38. Nurse Practitioners/cl, og, sn, ut [Classification, Organization & Administration, Statistics & Numerical Data, Utilization]

39. team function.mp.

40. endpoint.mp. or Endpoint Determination/

41. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40

42. 23 and 30 and 41

43. limit 42 to (english language and yr="1973 -Current")

****

Appendix G Risk of Bias of Included RCTs

Overall Risk of Bias of Included Studies (n=29)	Random sequence generation: selection bias	Allocation concealment: selection bias	Collection of objective outcome measure: detection bias	Outcome data at least > or = to 80% of sample: attrition bias	Outcomes completely reported in results: reporting bias	Other: includes any and all other biases found in RCT	**Low Risk of Bias / High Quality RCT**
Ganz, 2000[61]	U*	U*	Y	Y	Y	Y	Low
Pioro, 2001[71]	Y	Y**	Y	N	Y	Y	Low
Allen, 2002[44]	Y	Y	Y	N	Y	Y	Low
Cooper, 2002[62]	Y	Y	Y	Y	Y	Y	Low
Jones, 2002[66]	Y	U	Y	Y	Y	Y	Low
Ansari, 2003[45]	Y	U	Y	Y	Y	Y	Low
Hill, 2003[55]	Y	U	Y	Y	Y	Y	Low
Tranmer, 2004[46]	Y	U	Y	Y	Y	Y	Low
Fairall, 2005[8]	Y	Y	Y	Y	Y	U	Low
Williams, 2005[60]	Y	Y	Y	Y	Y	Y	Low
Goessens, 2006[47]	Y	N (Zelen design)	Y	Y	Y	U	Low
Nathan, 2006[49]	Y	U	Y	Y	Y	Y	Low
Johnson-Mallard, 2007[70]	Y	U	Y	Y	Y	Y	Low
Krichbaum, 2007[64]	Y	Y	Y	N	Y	Y	Low
Dierick-van Daele, 2009[67]	Y	Y	Y	Y	Y	Y	Low

McCarrier, 2009[7]	Y	U	Y	Y	Y	Y	Low
McCorkle, 2009[52]	Y	Y	Y	Y	Y	U	Low
Mitchell, 2009[54]	Y	U	Y	Y	Y	Y	Low
Ralston, 2009[6]	Y	Y	Y	Y	Y	Y	Low
ter Bogt, 2009 [56]	Y	U	Y	Y	Y	N	Low
Huizinga, 2010 [51]	Y	Y	Y	Y	Y	Y	Low
Schuttelaar, 2010 [59]	Y	Y	Y	Y	Y	Y	Low
Enguidanos, 2012 [65]	U	Y	Y	Y	Y	N	Low
Hannan, 2012 [69]	Y	U	Y	Y	Y	Y	Low
McClellan, 2012 [63]	U	Y	Y	Y	Y	Y	Low
Kim, 2013 [53]	Y	U	Y	Y	Y	Y	Low
Sawatsky, 2013 [48]	Y	U	Y	Y	Y	Y	Low
Berkhof, 2014 [50]	Y	U	Y	N	Y	Y	Low
Mertens, 2014 [68]	U	Y	Y	Y	Y	Y	Low

***** Baseline measurements and randomization occurred at a subsequent in-person visit. Participants were stratified by age (< or = to 55 years versus >55 years) and tamoxifen use (currently used versus not used) as part of the randomization procedure; at baseline visit, patient obtained random assignment, Table 1, Ganz (2000), p. 1055.

- Sequence Generation (selection bias): The simple statement that "patient obtained random assignment" is insufficient to be confident that the allocation sequence was genuinely randomized (unbiased).
- Allocation Concealment (selection bias): Proper concealment of the allocation sequence is necessary to secure strict implementation of the allocation sequence without foreknowledge of intervention assignments. Allocation concealment refers to *techniques used to implement the sequence* shielding those who admit participants to a study from knowing the upcoming assignments.[15]

** Post-randomization breach in patient assignment: crossover of 89 NP patients to house-staff ward; only 104 patients were admitted to NP ward after randomization of 193 patients to NP ward. Reasons noted:
1) unavailable beds on NP ward (almost 1/3 of cross-overs); 2) request of attending doctors (more than 1/5 of cross-overs) with flexibility to pre-empt randomization based on doctors' concerns that certain patients that may be 'too sick' / require 'off-hours' monitoring, during which time NPs were unavailable; and 3) request of NPs, based on concerns for adequate staffing; the RCT utilized 2.5 full-time-equivalent NPs, on the unit from 0730 - 2000 on weekdays and for morning rounds on weekends (Pioro, 2001, p. 29).

However, it is unclear as to whether patient assignment post-randomization, truly represents selection bias, a systematic error that over or underestimates the intervention effect.[15] An Unclear judgement may not be penalized with a No judgement. Further, colleagues Donald et al. (2014, Figure 2, p. 13) categorized this RCT to contain a low risk of selection bias in their systematic review on cost-effectiveness of NPs and CNSs.[38]

Appendix H Risk of Bias of Excluded RCTs

Overall Risk of Bias of *Excluded* Studies (n=27)	Random sequence generation: selection bias	Allocation concealment: selection bias	Collection of objective outcome measure: detection bias	Outcome data at least > or = to 80% of sample: attrition bias	Outcomes completely reported in results: reporting bias	Other: includes any and all other biases found in RCT	**Over-all Risk of Bias**
Porrett (2001) *A prospective randomized trial of consultant-led injection sclerotherapy compared NP-led non-invasive interventions in the management of patients with haemorrhoids.* Colorectal Disease	U	U	N	N	N	N	High Risk
Vernooij (2012) *Internet based vascular risk factor management for patients with clinically manifest vascular disease: randomised controlled trial.* BMJ	U	U	N	Y	Y	N, N, N	High Risk
Hanrahan (2014) *A pilot RCT: testing a transitional care model for acute psychiatric conditions.* Journal of the American Psychiatric Nurses Association	Y	U	N	Y	Y	N, N, N	High Risk

Wheelock (2015) *SIS.NET: a RCT evaluating a web-based system for symptom management after treatment of breast cancer.* Cancer	U	U	Y	N	N	N, N,	High Risk
Beckham (2007) *Motivational interviewing with hazardous drinkers*. Journal of American Academy Nurse Practitioners	Y	U	N	Y	Y	N	Moderate
Dyar (2012) *A NP directed intervention improves the quality of life of patients with metastatic cancer: results of a randomized pilot study,* Journal of Palliative Medicine	U	U	Y	N	Y	N	Moderate
Kinnersley (2007) *Randomised controlled trial of nurse practitioner versus general practitioner care for patients requesting "same day"*	Y	N	Y	N	Y	Y	Moderate

consultations in primary care. BMJ							
Mundinger (2000) *Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial.* JAMA	U	Y	N	N	Y	N	Moderate
Venning (2000) *Randomised controlled trial comparing cost effectiveness of general practitioners and nurse practitioners in primary care.* BMJ	Y	N	N	N	Y	Y	Moderate
Whitaker (2001) *Botulinum toxin for people with dystonia treated by an outreach NP: a comparative study between a home and a clinic treatment service.* Archives of Physical Medicine and Rehabilitation	Y	U	N	Y	Y	N	Moderate
Oslin (2002) *Alcoholism treatment adherence: older age predicts better adherence and drinking outcomes.* American Journal Geriatric Psychiatry	U	U	U	N	N	Y	Moderate
Heitkemper (2004) *Self-management for women with irritable bowel*	U	N	U	U	Y	N	Moderate

syndrome. Clinical Gastroenterology and Hepatology							
Krein (2004) *Case management for patients with poorly controlled diabetes: a randomized trial*. American Journal of Medicine	Y	N	U	Y	Y	N	Moderate
Limoges & Rickabaugh (2004) *Evaluation of TENS during screening flexible sigmoidoscopy*. Gastroenterology Nursing	U	N	N	Y	Y	U	Moderate
Purath (2004) *A brief intervention to increase physical activity in sedentary working women*. Canadian Journal Nursing Research	N	N	Y	Y	Y	N	Moderate
Robbins (2006) *Girls on the move program to increase physical activity participation*. Nursing Research	Y	U	N	Y	Y	N	Moderate
Sledge (2006) *A randomized trial of primary intensive care to reduce hospital admissions in patients with high utilization of inpatient services*. Disease Management	Y	Y	Y	N	Y	N	Moderate
Smith (2006) *Primary care clinicians treat patients with medically*	Y	N	Y	Y	U	N	

unexplained symptoms: a RCT. Journal General Internal Medicine							Moderate
Marion (2009) *The well woman program: a community-based randomized trial to prevent STIs in low-income African American women*. Research in Nursing & Health	Y	N	Y	N	Y	Y	Moderate
Whittemore (2009) *Translating the diabetes prevention program to primary care: a pilot study*. Nursing Research	Y	U	N	Y	Y	N	Moderate
Stone (2010) *Active care management supported by home tele-monitoring in veterans with type 2 diabetes: the Dia-Tel randomized controlled trial.* Diabetes Care	Y	N	Y	Y	Y	N	Moderate
Limoges-Gonzalez (2011) *Comparisons of screening colonoscopy performed by a NP and gastroenterologists.* Gastroenterology Nursing	N	N	U	Y	U	U	Moderate
Beaver (2012) *An exploratory RCT comparing telephone and*	Y	U	Y	N	Y	N	Moderate

hospital follow-up after treatment for colorectal cancer. Colorectal Disease							
Bell et al. (2012) *Mobile phone-based video messages for diabetes self-care support.* Journal of Diabetes Science and Technology	N	U	Y	Y	Y	N	Moderate
Goldie (2012) *Nurse Practitioners in postoperative cardiac surgery: are they effective?* Canadian Journal of Cardiovascular Nursing	U	U	Y	N	Y	N	Moderate
Konkle-Parker (2012) *Pilot testing of an HIV medication adherence intervention in a public clinic in the Deep South.* Journal of the American Academy of Nurse Practitioners	U	U	Y	N	Y	N	Moderate

Appendix I: Endpoint Assessment per Endpoint Category and 10 Post Hoc Analyses

Table I-1 Clinical Endpoint-Outcomes

No statistically significant differences in 2 RS^ studies (positive results)
Adverse Events in *Internal Medicine Inpatients,* Acute RS
Total Number Acute Exacerbations in *Asthma Patients,* Outpatient RS

No statistically significant differences in IPT^^ study
Adverse Events in *Chronic Heart Failure Patients,* Outpatient IPT (pilot study)

Author, Year **RS^ / IPT^^** **Setting** **Study Population Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)		**Quality of Endpoint Assessment / Comments**
Pioro, 2001 [71] RS ^ Acute Inpatient 381 heterogeneous internal medicine inpatients 18–69 years, admitted for gastrointestinal, pulmonary, infectious, metabolic/ substance abuse, neurological, cardiovascular and "other" acute illnesses; study duration from hospital admission to 6 weeks post-discharge at single center teaching hospital, U.S.	*Intervention* = NP-based care (n=193) *Control*=House-staff care (n=188) Post-randomization breach in patient assignment for possible selection bias: crossover of 89 NP patients to house-staff ward, with 104 patients admitted to NP ward after randomization of 193 patients to NP ward. Reasons: unavailable beds on NP ward; house-staff & NPs' requests (see Appendix G)	*Adverse Events Transfers to ICUs, NP 3.6% House-staff 6.9% Difference -3.3% (95% CI -7.8, 1.2) p > 0.10 In-hospital mortality NP 1.6% House-staff 1.1% Difference 0.5% (95% CI -1.8, 2.8) p > 0.10 30-day post discharge mortality NP 3.6% House-staff 3.2% Difference 0.4 % (95% CI -3.2, 4.0) p > 0.10	>1 Hospital acquired complication NP 5.3% House-staff 8.6% Difference -3.3% (95% CI -8.4, 1.8) p > 0.10 Overall Adverse Events (including only transfers to ICUs, in-hospital mortality, and hospital-acquired complications) NP 7.5% House-staff 11.8% Difference - 4.3% (95% CI -10.2, 1.6) p > 0.10	Data obtained from medical records, hospital databases Incomplete reporting of raw data in Table 2: no fraction of patients comprising percentages was reported. It is unclear as to whether patient assignment post-randomization, truly represents selection bias, a systematic error that over or underestimates the intervention effect. An Unclear judgement may not be penalized with a No judgement.[15] (see Appendix G)

Nathan, 2006 [49] RS ^ Outpatient / Specialized Referral 154 outpatients > 16 years of age recently discharged from the hospital as a result of acute asthma; 6 months study duration post-discharge at hospital outpatient clinic, England	*Intervention* = NP care (n= 78) *Control* = Respirologist care (n=76)	*<u>Number acute asthma exacerbations at 6 months</u> NP 98/174 exacerbations Respirologist 76/174 exacerbations Difference 22 exacerbations p = 0.368 <u>4 types exacerbations</u> 1) Mean number hospital readmissions per patient NP 0.07 Respirologist 0.18 Relative risk of readmission = 0.40 (95% CI 0.14 to 1.12) p = 0.09 2) Emergency nebulization in accident & emergency departments, general practice, or by ambulance paramedics NP 35 times (17 different patients) Respirologist 16 times (10 different patients) No p-value reported	3) <u>Mean number of exacerbations per patient requiring any emergency treatment (hospital admission or emergency nebulization)</u> NP 0.59 Respirologist 0.43 Relative risk = 1.37 (95% CI 0.84 to 2.21) Non-significant difference (CI includes null value of 1) 4) IV or oral steroids during exacerbation (excluding patients using increased inhaled corticosteroids) NP 51.9% (27/52patients) Respirologist 48.1% (25/52 patients) Difference 3.8% p=0.572 Mean number exacerbations requiring IV/oral steroids per patient NP 1.18 Respirologist 0.91 Relative risk =1.30 (95% CI 0.93 to 1.81) Non-significant	No inconsistencies were found between data sources: patient diary card, emergency department attendance records, and general practice records Limited control for intervention effect, related to confounding factor of home nebulizers used by 'a few patients' to self-administer bronchodilators (Nathan, 2006, p. 53)
Ansari, 2003 [45] **Pilot RCT** with 2 levels of individual randomization IPT ^^ Outpatient / Specialized Referral 169 Chronic Heart Failure (CHF) patients were individually randomized into	*Notification Intervention* Beta-blocker advocacy Internists 10 Cardiologists 2 NPs 3 (n = 64 patients) *NP Facilitator Intervention* Initiation, titration, and stabilization of CHF patients on	<u>Adverse Events</u> 1) Hospitalizations / Emergency Room visits <u>Notification</u> 45% (29/64 patients) <u>NP Facilitator</u> 43% (23/54 patients) <u>Control</u> 49% (25/51 patients) p = 0.81	2) Mortality <u>Notification</u> 2% (1/64 patients) <u>Nurse Facilitator</u> 9% (5/54 patients) <u>Control</u> 14% (7/51 patients) p = 0.05 Only 1 outcome of death recorded in the notification group eliminates ability to statistically infer impact on mortality	Data regarding hospitalizations, ER visits, and deaths obtained from medical records and patient contact at 3-month intervals Information was collected on adverse events as an indicator of safety not efficacy (e.g. to confirm no increase in adverse events, vs an efficacious

3 groups 74 providers (internal medicine doctors, cardiologists and NPs) were also individually randomized into 3 groups, to decrease the likelihood of contamination, i.e. patients receiving care from their regular providers Median follow-up period = 12 months, at an academic medical center, U.S.	beta-blockers Internists 19 Cardiologists 3 NPs 3 (n=54 patients) *Control* Provider education regarding beta blocker guidelines Internists 16 Cardiologists 4 NPs 4 (n=51 patients)			reduction in adverse events)

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT)

Table I-2 Physiologic Surrogate Marker Endpoint-Outcomes

Statistically significant differences in 4 IPT^^ studies, 1 RS^ study

Blood Lipids in *Coronary Heart Disease Patients*, Outpatient IPT
CVD Risk Factors in *Cardiovascular Disease Patients*, Outpatient IPT
Glycated Hemoglobin in *Type 2 Diabetes Patients*, Outpatient IPT
Tuberculosis Detection (sputum microscopy / culture) in *Respiratory Disease Patients*, Primary Health Care IPT
Risk Factors Associated with Obesity: Systolic Blood Pressure and Fasting Glucose, in *Obese / Moderately Overweight Patients*, Primary Health Care RS (original study and post hoc analysis)

No statistically significant differences in 2 IPT^^ studies, 1 RS^ study

Glycated Hemoglobin in *Type 1 Diabetes Patients*, Outpatient IPT (pilot study)
Glycemic Relapse in *Type 2 Diabetes Patients*, Outpatient IPT
Plasma Viscosity in *Rheumatoid Arthritis Patients*, Outpatient RS

Author, Year **RS^ / IPT^^** **Setting** **Study Population, Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)		**Quality of Endpoint Assessment / Comments**
Allen, 2002 [44] IPT ^^ Outpatient / Specialized Referral 228 coronary heart disease (CHD) outpatients who received coronary artery bypass grafting (CABG) surgery or percutaneous coronary intervention (angioplasty) with hypercholesterolemia (low density lipoprotein cholesterol level > 2.59 mmol/L or total	*Intervention* = NP case management (individualized lifestyle and pharmacologic intervention) + Enhanced Usual Care (EUC) (n = 115) *Control* = Enhanced Usual Care (EUC) from primary providers &/or cardiologists including full lipid profiles at 4 weeks, 6 and 12 months after	* <u>Mean (SD) Lipid levels at 1 year</u> <u>Total Cholesterol</u> (TC) NP 4.1mmol/L (0.7) EUC 4.6mmol/L (0.6) Difference = 0.5 mmol/L p < 0.0001 *<u>Low-density lipoprotein cholesterol</u> (LDL-C, 'bad' cholesterol) NP 2.20 mmol/L (0.57)	*<u>Triglycerides</u> (TG) NP 3.57 mmol/L (1.53) EUC 4.25 mmol/L (1.79) Difference = 0.68 mmol/L p = 0.002 * <u>Achieved</u> **LDL-C treatment goal** < 2.59 mol/L NP 65% EUC 35% Difference 30% p = 0.0001 ***** <u>High-density lipoprotein</u>	High quality endpoint assessment from blood chemistry results of lab lipid profile reports <u>Attrition: 31%</u> 69%; 158/228 outpatients completed 12 mo. follow-up (77% NP patients; 62% UC patients) Control of hypercholesterolemia in patients who

cholesterol level > 5.18 mmol/L); intervention for one year post-discharge, at outpatient clinic of large tertiary hospital, U.S.	discharge, and goals for levels of lipoproteins, diet and physical activity (n =113)	EUC 2.67mmol/L (0.57) Difference = 0.47 mmol/L p < 0.0001	cholesterol (HDL-C, 'good' cholesterol) increased modestly in both groups	have undergone coronary revascularization can be improved by NP case management as per study
Goessens, 2006 [47] IPT ^^ Outpatient / Specialized Referral Cardiovascular disease (CVD) Peripheral arterial disease Abdominal aortic aneurysm Cerebrovascular disease Coronary heart disease (CHD) 236 CVD outpatients with two or more modifiable risk factors: smoking, hypertension, dyslipidemia, diabetes, obesity, hyperhomocysteinemia. Intervention for one year after randomization at a risk-factor management clinic in the University Medical Center (UMC) Utrecht, Netherlands	*Intervention* = NP at risk factor management clinic + usual care (n=119) *Control* = Usual Care (UC) by GP and treating vascular specialist (n=117)	Percent patients who achieved treatment goals at mean follow-up of 14 months (range 10-22) 1. LDL cholesterol treatment goal < or equal to 3.1 mmol/L NP 88 UC 67 OR 3.5 95% CI 1.5–8.6 2. Total cholesterol treatment goal < 5.0 mmol/L NP 79 UC 61 OR 3.3 95% CI 1.5–7.3	3. Systolic Blood Pressure treatment goal < 140 mmHg NP 63 UC 37 OR 2.7 95% CI 1.3–5.4 4. BMI treatment goal < 25 kg/m^2 NP 38 UC 24 OR 4.0 95% CI 1.2–13.1 Differences non-significant: Diastolic BP, HDL-C, Triglycerides, Fasting Blood Glucose, Homocysteine, Waist Circumference, Smoking	Patients were randomized before informed consent was obtained, according to Zelen design, yet treatment consent is always sought before actual intervention, Torgerson & Roland (1998) Physical exam (by NP, GP or vascular specialist) for CV risk profile at 1 year, measured in risk factor management clinic. Attrition 31% (71/236) patients: 61 patients gave no informed consent post randomization (24 patients randomized to intervention & 37 to control); 10 patients did not complete study: 4 deaths / group, 1 moved, & another developed co-morbidity

Ralston, 2009 [6] IPT ^^ Outpatient / Specialized Referral 83 Type II Diabetes Mellitus outpatients, 18 - 75 years with glycosylated hemoglobin (GHb) in prior year > or = to 7%, at least 2 clinic visits in prior year 12 month intervention period, at the University of Washington General Internal Medicine Clinic, a teaching clinic that provides care to 7, 707 patients, staffed by 25 faculty, 48 residents, and an NP, for case management of chronic disease patients, U.S. (Ralston, 2009, p. 234)	*Intervention* = NP coordination of Web-based care + usual care (n=42) *Control* = usual care (UC) from an internal medicine physician (n=41) All providers used the same Electronic Medical Record (EMR)	*<u>Physiologic markers at 12 months</u> Target: glycosylated hemoglobin < 7% <u>Absolute change in glycosylated hemoglobin</u> NP Web intervention 33% at target UC 11% at target Difference = 22% p =0.03	<u>At 12 months mean changes in risk factors</u> between groups were non-significant (no individual data shown) • Systolic BP p = 0.84 • Diastolic BP p = 0.96 • Total cholesterol p = 0.38	High quality endpoint assessment using GHb rapid immunoassays in Bayer Lab DCA-2000+ analyzer Incomplete reporting of raw data in Table 3: no fraction of patients comprising percentages was reported Patient / provider Web access to same Electronic Medical Record (EMR) can improve glycemic control in Type II Diabetes Mellitus outpatients, as per study
ter Bogt, 2009 [56] American Journal of Preventive Medicine Groningen Overweight and Lifestyle (GOAL) study RS ^ Primary Health Care (PHC) 457 PHC patients with BMI 25- 40, and either hypertension, dyslipidemia or both; one year study period at 11	*Intervention* = low-intensity (for prevention of additional weight gain) lifestyle counseling by NPs: 4 individual visits and 1 feedback session by telephone over one year (n =225) *Control* = usual GP care (n = 232) Physical exam	<u>Physiologic markers at 1 year</u> <u>Blood pressure (BP)</u> 1) <u>Reduction in SBP (mmHg) in obese men</u> (BMI > or = 30 kg/m^2) NP -14 UC -5 Difference = 9 mmHg reduction in SBP p < 0.05 <u>2) Mean reduction (SD) in SBP (mmHg) in</u>	<u>Blood lipids</u> <u>1) Mean change (SD) in total cholesterol</u> (mmol/L) <u>in women</u> (BMI 25-40 kg/m^2) NP + 0.02 (0.8) UC - 0.06 (0.8) Absolute difference = 0.08 mmol/L non-significant <u>2) Mean change (SD) in total cholesterol</u> (mmol/L) <u>in men</u> (BMI 25-40 kg/m^2)	Physical exam by a trained research team; blood samples were collected by the trained research team; samples were analyzed in a central lab using certified lab assays General linear model (GLM) showed that gender is an effect modifier; data thus reported separately for men &

general practice locations (1-7 GPs and 1-3 NPs per location), Netherlands Obesity BMI > or = to 30 kg/m^2 Moderately Overweight BMI 25 - 30 kg/m^2	done by a trained research team that measured body weight, length, waist circumference, and blood pressure	men (BMI 25 -40 kg/m^2) NP -8.5 (16.8) UC -5.3 (12.7) Difference non-significant 3) Mean reduction (SD) in SBP (mmHg) women (BMI 25 - 40 kg/m^2) NP -5.3 (20.1) UC -2.2(16.5) Difference = 3.1 mmHg non-significant	NP - 0.18 (0.6) UC + 0.03 (0.7) Absolute difference = 0.21 mmol/L non-significant Mean reduction (SD) Fasting Glucose (mmol/L) at 1year Women (BMI 25 - 40 kg/m^2) NP - 0.08 (0.6) UC- 0.11 (0.5) Difference = 0.03 mmol/L non-significant Men (BMI 25-40 kg/m^2) NP -0.03 (0.6) UC -0.05 (0.8) Difference = 0.02 mmol/L non-significant	women Attrition 9% (41/457); 24 intervention patients + 17 control patients = 41 patients withdrew by 1 year end of trial A low-intensity lifestyle intervention can improve systolic blood pressure in obese men as per study
#ter Bogt, 2011 [80] **Post Hoc Analysis** to ter Bogt (2009); Archives of Internal Medicine RS ^ Primary Health Care (PHC) 3-year follow-up to the Groningen Overweight and Lifestyle (GOAL) study; following the initial one year study, 1 individual visit and 2 feedback sessions occurred over the next 2 years, Netherlands	*Intervention* = low-intensity (for prevention of additional weight gain) lifestyle counseling by NPs (n=171) patients *Control* = usual GP care (n=186) patients	BP, blood lipid and fasting glucose levels after 3 years Mean change (SD) in fasting glucose (mmol/L) NP −0.02 (0.49) UC 0.10 (0.53) p = 0.02	Mean change (SD) total cholesterol (mmol/L) NP 0.07 (0.92) UC −0.05 (0.93) p = 0.15 Mean change (SD) Systolic BP (mm Hg) NP −5.9 (17.3) UC −3.8 (14.5) p = 0.38	Data on secondary outcomes of physiologic markers at 3 year follow-up not stratified by gender while general linear model (GLM) from the original study showed that gender is an effect modifier. A low-intensity lifestyle intervention may sustain improved fasting glucose levels for obese patients 3 years after intervention.

Fairall, 2005 [8] Cluster RCT, unit of random allocation = primary health care (PHC) clinic IPT ^^ Primary Health Care (PHC) <u>Priority Respiratory Diseases</u>: LRTI (lower respiratory tract infection), URTI (Upper RTI), asthma, tuberculosis (TB), HIV, and chronic obstructive pulmonary disease (COPD) 40 primary health care (PHC) clinics staffed by NPs were randomized, including 1,999 patients with cough or difficult breathing on presentation, or within past 6 months; three month study period, South Africa	*Intervention* = PALSA (Practical Approach to Lung Health in South Africa) Intervention, an educational outreach program of expanded prescribing provisions with locally tailored guidelines, implemented by NPs 20 clinics randomized to outreach intervention, including 1000/1999 patients *Control* = Usual NP Care, with no new training in educational outreach program 20 clinics randomized to usual care, including 999/1999 patients	*<u>Case detection of tuberculosis (TB) at 3 months</u> Educational Outreach Intervention 6.4% (57/892) Control 3.8% (34/890) Denominator limited to all patients who had not been diagnosed with tuberculosis (TB) before educational outreach started OR =1.72 (95% CI 1.04 to 2.85) p= 0.04 ICC=0.007		Limited data collection related to patient self-report for unknown quantity of data: results of sputum microscopy or culture documented on TB card, or by patient report Patients and fieldworkers were blind to the intervention status of each clinic Educational outreach with integrated case management can improve case detection of TB without extra staff, in resource poor setting as per study
McCarrier, 2009 [7] IPT ^^ Outpatient / Specialized Referral **Pilot RCT** 78 Type 1 diabetes mellitus outpatients randomized, 21 -49 years with at least one A1C test > or = to	*Intervention* = NP coordination of Web-based care + usual care (n =42) *Control* = usual care (UC) from team at Diabetes Care Center (DCC) (n = 36)	*<u>Mean (SD) change hemoglobin A1c values at 1 year</u> NP - 0.37 (1.3) UC: + 0.11 (1.4) Absolute difference = 0.48 (95% CI -1.22 to 0.27) p= 0.160		High quality endpoint assessment based on rapid immunoassay tests, obtained from the electronic medical record, accessible to both patient / provider, for Web-based diabetes case management Small sample size with

7% in previous 12 months; one year intervention period at the Diabetes Care Center (DCC): multidisciplinary practice team includes physicians, NPs, on-site pharmacists, nurse educators, nutritionists, and mental health professionals, affiliated with the main University of Washington Medical Center, U.S.				attrition at 17% (13/78), 7 patients from UC group + 6 patients from NP group, limited ability to detect statistically and clinically significant differences
Huizinga, 2010 [51] IPT ^^ Outpatient / Specialized Referral 165 Type 2 diabetes mellitus outpatients, 18-75 years, initially referred to Diabetes Improvement Program (DIP) for poor glycemic control (A1c > 8%) with subsequent successful improvement in glycemic control. DIP success defined as ≥ 1% decline in A1c during DIP. Two year study intervention delivered offsite via telephone; based at an academic medical centre, U.S.	*2 Intervention Groups* Usual Care + NP phone contact over 2 years: 1) Quarterly contact (every 3 months) (n = 55) 2) Monthly contact (n =55) *Control* = Usual care (UC) through routine follow-up in Diabetes Improvement Program (n = 55)	*Glycemic relapse, defined as an increase in HbA1c of > or = to 1% over baseline, at 2 years Quarterly contact 21% (10/48) patients relapsed Monthly contact 29% (15/52) patients relapsed UC 25% (12/48) patients relapsed p=0.83	Prevalence of relapse did not differ between groups over follow-up time, nor did the cumulative incidence of relapse differ between treatment groups (p = 0.72)	Precision & accuracy of HbA1c measurement according to the DCCT (Diabetes Control & Complications Trial) method, National GlycoHb Standardization Program Test was performed in a study population already motivated with previous glycemic control. Study protocol did not contain care strategies for patients who relapsed, and was not powered for sub-group analysis between its 3 groups

Hill, 2003 [55] RS ^ Outpatient / Specialized Referral 80 Rheumatoid Arthritis (RA) outpatients, 18 years or older, to rheumatology clinic on at least three previous occasions; study period of 12 months, at a traditional rheumatology outpatient clinic managed by junior hospital doctors (JHDs) within a large teaching hospital, England	*Intervention* = rheumatology NP (RNP) care (n =39) *Control* = junior hospital doctor (JHD) care (n= 41)	Plasma Viscosity at 48 weeks (Inflammation, accompanied by changes in plasma protein, can increase plasma viscosity) Median value mPa (range) RNP 1.62 mPa (1.49– 1.85) JHD 1.63 mPa (1.50–1.97) Difference nonsignificant		Plasma viscosity (cells / solid matter e.g. protein, suspended in plasma of blood) laboratory test has high sensitivity (little alteration may be pathologically important) but low specificity, Késmárky (2008)

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT) #Post Hoc Analysis

Table I-3 Symptom Severity, Functional Status, Behaviour/Lifestyle Change

i. Symptom Severity *(symptom - indication of disease or change in condition[3])*

Statistically significant differences in 4 IPT^^ studies

Pain Ratings and Cancer-Specific QOL in *Advanced Cancer Patients,* Outpatient IPT
Menopause Symptoms in *Breast Cancer Survivors* with abruptly recurred menopause, Outpatient IPT
Cancer-Specific QOL in *Post-operative Women with Suspected Ovarian Cancer,* Outpatient IPT
Body Weight Loss and Waist Circumference in *Obese / Moderately Overweight Patients*, Primary Health Care RS
Symptom Severity / Cure in *Patients with Incontinence*, Primary Health Care IPT (original study and post hoc analysis)
Fatigue in *Rheumatoid Arthritis Patients*, Outpatient RS
Post-stroke Depression in *Ischemic Stroke Patients*, Outpatient IPT

No statistically significant differences in 4 IPT^^ studies, 5 RS^ studies (positive results)

Disease-specific Symptoms St. George Respiratory Questionnaire in *COPD Patients,* Outpatient IPT (pilot study)
Post-operative Symptoms in *Cardiac Surgery Patients*, Outpatient IPT
Post-operative Symptoms in *CABG Patients,* Outpatient IPT
Post-operative Symptoms in *Hip Fracture Surgery Patients*, Outpatient IPT (pilot study)
Disease-specific Symptoms St. George Respiratory Questionnaire in *Acute Asthma Patients,* Outpatient RS
Symptoms *Internal Medicine Inpatients* six weeks post-discharge, Acute RS
Symptom Severity in *Minor Injury Emergency Department Patients,* Acute RS
Disease Activity, Psychological Status, Pain *Rheumatoid Arthritis Patients,* Outpatient RS
Eczema-specific Quality of Life *Infants / Children with Atopic Dermatitis*, Outpatient RS

ii. Functional Status

Statistically significant differences in 3 IPT^^ studies and 1 RS^ study

Health Status *COPD Patients,* Outpatient IPT (pilot study)
Sexual Functioning in *Breast Cancer Survivors* with abruptly recurred menopause, Outpatient IPT

No statistically significant differences in 1 IPT^^ and 3 RS^ studies

Functional Impairment (chemotherapy) in *Advanced Cancer Patients*, Outpatient IPT
ADL/IADLs in *Internal Medicine Inpatients* six weeks post-discharge, Acute RS
Percentage Return to Normal Function *Soft Tissue Injury Emergency Department Patients,* Acute RS
Peak Flow in *Acute Asthma Patients,* Outpatient RS

iii. Behaviour / Lifestyle Change

Statistically significant differences in 2 IPT^^ studies, 1 RS^ study

Diet and Exercise in *Coronary Heart Disease Patients*, Outpatient IPT
Alcohol and Drug Use in *Low-Income Addictions Patients*, Primary Health Care IPT
Physical Activity in *Obese / Moderately Overweight Patients*, Primary Health Care RS (post hoc analysis)

No statistically significant differences in 1 IPT^^ study

Distress; Hospital Anxiety Depression in *Advanced Cancer Patients,* Outpatient IPT

Symptom Severity, Functional Status, Behaviour/Lifestyle Change Endpoint-Outcomes

Author, Year **RS^ / IPT^^** **Setting** **Study Population, Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)		**Quality of Endpoint Assessment / Comments**
Allen, 2002 [44] IPT ^^ Outpatient / Specialized Referral 228 coronary heart disease (CHD) outpatients who received coronary artery bypass grafting (CABG) surgery or percutaneous coronary intervention (angioplasty), with hypercholesterolemia (low density lipoprotein cholesterol level > 2.59 mmol/L or total cholesterol level > 5.18 mmol/L); intervention for one year post-discharge, at outpatient clinic of large tertiary hospital, U.S.	*Intervention=* NP case management (individualized lifestyle and pharmacologic intervention) + Enhanced Usual Care (n = 115) *Control =* Enhanced Usual Care (EUC) from primary providers &/or cardiologists including full lipid profiles sent to patients and their physicians at 4 weeks, 6 and 12 months after discharge, including goals for levels of lipoproteins, diet and physical activity (n =113)	<u>Diet and exercise at 1 year</u> <u>Mean dietary intake (SD) in calories</u> <u>Total fat</u> NP 33.2% (+ or - 6.7%) EUC 34.6% (+ or - 6.5%) Difference 1.4% p = 0.009 <u>Saturated Fat</u> NP 10.1% (2.2%) EUC 11.0% (2.3%) Difference 1.1% p = 0.004	<u>Dietary Cholesterol</u> (mg) NP 254.2 (99.8) EUC 292.0 (104.9) Difference 37.8 p = 0.006 <u>Dietary fiber</u> NP 22.2 (7.2) EUC 21.3 (5.7) Difference 0.9 p = 0.28 <u>Exercise</u> at a level of 6 MET (metabolic equivalent) hours/week or more NP 40% (46/115) EUC 26% (29/113) Difference 14% p = 0.02	Endpoint assessment based on the Block Health Habits and History questionnaire food frequency instrument, reviewed by study dietician; and the validated Physical Activity questionnaire that quantified weekly energy expenditure in metabolic equivalent (MET) hours Incomplete reporting of raw data in Table II: no fraction of patients comprising percentages of dietary intake was reported. Diet and exercise in CHD patients with hypercholesterolemia can be improved by a NP case management program as per study

ter Bogt, 2009 [56] American Journal of Preventive Medicine; Groningen Overweight and Lifestyle (GOAL) study RS^ Primary Health Care (PHC) 457 PHC patients with BMI 25- 40 kg.m^2, and either hypertension, dyslipidemia or both; one year study period at 11 general practice locations (1-7 GPs and 1-3 NPs per location), Netherlands Obesity BMI > or = to 30 kg/m^2) Moderately Overweight BMI 25 - 30 kg/m^2	*Intervention* = low-intensity lifestyle counseling by NPs over one year: 4 individual visits and 1 feedback session by telephone (n =225) The relatively low intensity of the lifestyle counseling strategy was only expected to prevent (further) weight gain or establish marginal weight loss *Control* = usual GP care (n = 232)	***Percentage change in body weight** at 1 year NP -1.9% (95% CI -2.5, -1.2) 200/225 patients UC -0.9% (95% CI -1.5, -0.2) 214/232 patients Difference 1.0% p < 0.05 *Weight losers (successful) and stabilizers (percentage of subjects who gained less than 1% body weight from baseline to 1 year) Women NP 72.8% (75/103) patients UC 64.0% (73/114) patients Difference 8.8% p < 0.05 Men NP 80.6% (79/98) patients UC 65.3% (66/101) patients Difference 15.3% p < 0.05	Mean (SD) Waist circumference (cm) at 1 year Women NP -2.0 (7.8) (103/225) patients UC -1.5 (6.8) (114/232) patients Difference 0.5 Non-significant Men NP -2.8 cm (6.2) (98/225) patients UC -0.9 cm (4.5) (101/232) patients Difference 1.9 p < 0.05	Endpoint assessment based on physical exam by trained research team In non-medically indicated patients, the NP lifestyle counseling was explicitly aimed at weight stabilization, with the hypothesis of study being that an early focus on preventing (progression of) overweight and comorbidities through weight stabilization vs weight loss, may be more successful in the long term
#ter Bogt, 2011 [80] Archives of Internal Medicine **Post Hoc Analysis** to ter Bogt (2009) RS ^ Primary Health Care (PHC) 3-year follow-up to the Groningen Overweight and Lifestyle (GOAL) study, Netherlands	*Intervention* = low-intensity (for prevention of additional weight gain) lifestyle counseling 1 individual visit and 2 feedback sessions occurred over 2 years following the original RCT (n=171) *Control* = usual GP care (n=186)	Mean (SD) percentage change in body weight at 3 years NP −1.2 (5.8) (171/171) patients UC −0.6 (5.6) (186/186) patients p = 0.37	Mean (SD) change in waist circumference (cm) at 3 years NP −0.8 (7.1) (169/171) patients UC 0.4 (7.2) (182/186) patients p = 0.11	Endpoint assessment based on physical exam by trained research team Data at 3 year follow-up was not stratified by gender while the general linear model from the original study showed that gender is an effect modifier

#ter Bogt, 2011 [82] Public Health Nutrition **Post Hoc Analysis** to ter Bogt (2009) RS ^ Primary Health Care (PHC) 1 year follow-up to the original Groningen Overweight and Lifestyle (GOAL) study; post hoc included 341 GOAL patients who completed a Food Frequency and the Physical Activity Questionnaire, Netherlands	*Intervention* = low-intensity lifestyle counseling from NPs (n=169) *Control* = usual GP care (n=172)	<u>Physical activity at 1 year</u> Mean change in walking (minutes/week) from baseline to end of study at 1 year NP 33 min/week (95% CI 3, 63) UC -5 min/week (95% CI -28, 18) p = 0.05	<u>Diet at 1 year</u> No significant differences in changes to nutrient intake between groups General linear model from original study showed that gender is an effect modifier; yet data at 1 year follow-up was not stratified by gender	Endpoint assessment based on validated questionnaires: SQUASH (Short Questionnaire to Assess Health-Enhancing Physical Activity) and FFQ (food frequency questionnaire) at baseline and after 1 year A lifestyle intervention can improve obese patients' physical activity (walking, minutes/week), as per study, although data is limited by self-report
#Driehuis, 2012 [84] Patient Education and Counseling **Post Hoc Analysis** to ter Bogt (2009) RS ^ Primary Health Care (PHC) Three-year follow-up on 338 GOAL patients who completed the Food Frequency Questionnaire and/or the 'Short Questionnaire to Assess Health-enhancing physical activity' at 3 years, Netherlands	*Intervention* = low-intensity lifestyle counseling from NPs for three years. In the 2 years after the 1 year GOAL study, patients had one meeting with the NP and received two feedback phone calls each year (n=162) *Control* = usual GP care (n=176)	<u>Physical Activity at 3 years</u> Mean change (SD) in total physical activity (minutes/week) between baseline and 3 years NP -167 (1321) 111/ 162 patients UC -92 (1218) 137/176 patients p = 0.387	<u>Diet at 3 years</u> Mean change (SD) in total daily energy intake (kJ/day) between baseline and 3 years NP -587 (2059) 158/162 patients UC -523 (2114) 172/176 patients p = 0.737	Endpoint assessment based on validated questionnaires: SQUASH (Short Questionnaire to Assess Health-Enhancing Physical Activity) and FFQ (food frequency questionnaire) at baseline and after 3 years Reduction of intervention intensity to one meeting and two feedback phone calls per year, likely contributed to relapse of total physical activity in both groups

Berkhof, 2014 [50] IPT ^^ Outpatient / Specialized Referral **Pilot study** 100 chronic obstructive pulmonary disease (COPD) outpatients > or = to 40 years, COPD GOLD stage > or = to 2 (Global initiative for staging Obstructive Lung Disease: 1 = mild; 4 = very severe), smoking history >10 pack-years 2 year study at a large teaching hospital, Netherlands	*Intervention* = patient-initiated outpatient visits with pulmonary NP upon increase of symptoms (dyspnea, cough, sputum, hemoptysis, or thoracic pain); NP followed an 'on-demand protocol' that included consult with pulmonologist for urgent problems (n =49) *Control*= usual care (UC) of traditional outpatient visits initiated by pulmonologist, to the pulmonologist or the pulmonary NP (n=51)	*****<u>Mean (SE) deterioration in COPD status</u> at 2 years Clinical COPD Questionnaire (CCQ) scores range from 0 to 6; lower score signifying better health status; minimal clinically important difference (MCID) of CCQ total score is 0.4 NP 0.14 (+ or - 0.14) 40/49 patients UC 0.58 (+ or - 0.16) 29/51 patients Difference = - 0.44 (+ or - 0.21) 95% CI -0.87 to -0.023 p = 0.04 meeting the MCID for a clinically relevant effect <u>Median time to 1st exacerbation COPD (in 1^0 & 2^0 care) at 2 years</u> NP 307 days + or - 61.6 days (95% CI 186.3 to 427.7) UC 335 days + or - 60.2 days (95% CI 217.0 to 453.0) Difference 28 days p = 0.40	<u>Mean (SE) St. George's Respiratory Questionnaire (SGRQ), symptom domain</u> at 2 years (higher score on SGRQ = worse health status; minimal clinically important difference (MCID) of SGRQ total score is 4) NP 2.6 (3.0), on 38/49 patients UC 10.3 (3.4) 30/51patients Difference of 7.7 (4.6) 95% CI -16.8 to 1.4 p = 0.10 meeting MCID for a clinically relevant effect	Endpoint assessment for <u>disease-specific</u> quality of life based on reliable and valid tools: 1) Clinical COPD Questionnaire (CCQ) 2) St. George Respiratory Questionnaire (SGRQ) Results are exploratory: the on-demand system had not been investigated before in COPD patients Less deterioration in disease-specific health status can occur in a patient - initiated system of on-demand NP care as per study, although endpoint assessment of time to exacerbation was based on self-reported data
Hill, 2003 [55] RS^ Outpatient / Specialized Referral 80 Rheumatoid Arthritis (RA) outpatients, 18 years or older, to rheumatology clinic on at least three previous occasions; study period of 12	*Intervention* = rheumatology NP (RNP) care (n =39) *Control* = junior hospital doctor (JHD) care (n= 41)	*<u>Disease Activity Score (DAS28)</u> <u>Week 24</u> NP 35/39 patients JHD 34/41patients <u>Scores Unchanged</u> NP 19 patients JHD 25 patients <u>Scores Worsened</u> NP 6 patients JHD 5 patients <u>Scores Improved</u> NP 10 patients	<u>Week 48 Physical function Median (range)</u> NP 3.0 (0.8 – 8.2) JHD 3.8 (0.4 – 7.6) Difference nonsignificant <u>Week 48 Psychological status Median (range)</u> NP 2.7 (0.7 – 7.5) JHD 2.5	Endpoint assessment based on the DAWN Visual DAS28 calculator, and the Arthritis Impact Measurement Scales (AIMS) validated by Meenan et al. (1980) modified for British use (Hill et al., 1990) Patient assessments were

months, at a traditional rheumatology outpatient clinic managed by junior hospital doctors (JHDs) within a large teaching hospital, England		JHD 4 patients, no p-value reported <u>Week 48</u> NP 36/39 patients JHD 35/41patients <u>Scores Unchanged</u> NP 19 patients JHD 22 patients <u>Scores Worsened</u> NP 6 patients JHD 7 patients <u>Scores Improved</u> NP 11 patients JHD 6 patients no p-value reported	(0.2 – 6.7) Difference nonsignificant <u>Week 48 Pain, Median (range)</u> NP 5.7 (2.0 - 9.0) JHD 6.0 (1.5-9.5) Difference non-significant <u>Week 48 Length of morning stiffness (minutes), Median (range)</u> NP 60 (0–600) JHD 37.5 (0-270) Difference 22.5 nonsignificant <u>Week 48 Fatigue (minutes) Median value (range)</u> NP 60 (0–600) JHD 270 (0-600) p=0.02	undertaken by an independent research assistant, blind to group allocation Incomplete data regarding number of patients per group for comparison of measure fatigue, based on self-reported data in absence of formal measurement tool Multiple JHDs were involved in the study versus only one RNP resulting in bias associated with the NP (with 1 NP, cannot calculate variability through SD, for integration into effect estimate calculations)
Kim, 2013 [53] IPT ^^ Outpatient / Specialized Referral 108 advanced cancer outpatients, 20 - 80 years diagnosed with stage IV advanced solid tumor, moderate level of cancer-related pain (Visual Analog Scale score ≥4 out of 10 over	*Intervention* = usual care + daily phone monitoring (tele-monitoring) by NP (n = 54) *Control* = usual care (UC) of standardized pain education by NP in both study arms at first visit (n = 54)	*<u>Reduction in average pain ratings at 1 week</u>, Brief Pain Inventory (0 = no pain; > or = to 4= average pain; 10 = 'pain as bad as you can imagine') Number patients experiencing average pain intensity at 1 week NP 19% (10/54) UC 35% (19/54) Difference 16% p = 0.02 <u>1 week Functional impairment, mean (SD)</u> (Karnofsky performance score, 100 is "perfect" health and 0 is death) NP 66 (8.0) UC 65 (9.2)	<u>1 week % patients ≥ score of 4 on Distress Thermometer</u> (0 = not distressed, to 10 = extremely distressed) NP 83% (45/54) UC 91 % (49/54) Difference 8 % p = 0.09 <u>European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire</u> (EORTC QLQ-C30) <u>Physical function, mean (SD) at 1 week</u> (higher scores	Endpoint assessment based on the Wisconsin Brief Pain Inventory (BPI) , Hospital Anxiety Depression Scale, Distress Thermometer and the Karnofsky performance score, all standardized & well-validated All calculations were reported to have used actual per protocol data, with report of no adjustments made for missing data

last 24 h), and life expectancy >1 month; intervention period of 1 week at an outpatient pain clinic, South Korea		Difference 3 p = 0.68 <u>1 week % patients with score≥ 11, Hospital Anxiety Depression Scale</u> (0 – 7 = normal, 8 – 10 = borderline abnormal, 11 – 21 = abnormal) NP 57% (31/54) UC 54% (29/54) Difference 3% p = 0.34	represent higher levels of functioning) NP 56 (23) UC 55 (21) p = 0.03 Differences in all other component scores of the EORTC QLQ-C30 were non-significant	
Ganz, 2000 [61] IPT ^^ Outpatient / Specialized Referral 76 breast cancer survivors with abruptly recurred menopause symptoms due to discontinued estrogen replacement therapy (ERT) related to breast cancer; intervention period of 4 months at an outpatient clinic, U.S.	*Intervention* = comprehensive menopausal assessment or CMA: targets highly symptomatic women with the goal of reducing symptoms & improving quality of life, through education, counseling, & focus on non-ERT interventions; delivered by NP (n=37) *Control* = usual care (UC) +1 contact from research assistant at 2 months asking of therapies used for symptom management (n= 39)	*<u>Mean change (reduction) from baseline to 4 months in menopause symptom-scale score</u> NP 0.61 (95% CI 0.40–0.82) 33/37 patients UC 0.19 (95% CI −0.06 to 0.44) 39/39 patients p = 0.0004	<u>Mean change from baseline to 4 months sexual functioning scale</u> (Cancer Rehabilitation Evaluation System, CARES) NP 0.38 (95% CI 0.05–0.71) 33/37 patients UC 0.015 (95% CI −0.37 to 0.40) 39/39 patients p = 0.04	Endpoint assessment based on the Menopausal Symptom Scale Score for seven symptoms, adapted for this study from the Breast Cancer Prevention Trial Symptom Checklist Instead of using intention to treat analysis, estimation of intervention efficacy was made according to methods described by Angrist JD, Imbens GW, Rubin DB. *Identification of causal effects using instrumental variables*. J Am Stat Assoc 1996 (Ganz, 2000, p. 1056)

McCorkle, 2009[52] IPT ^^ Outpatient / Specialized Referral 149 post-surgical outpatients 21 years or older, suspected primary diagnosis of ovarian cancer after abdominal surgery, prognosis of at least 6 months, with an order to initiate chemotherapy Contact with study patients made at private homes or by telephone, U.S.	*Intervention* = 18 contacts by an oncology NP, supported by psychiatric NP (PSYNP) consults (32/74 intervention patients) when warranted for high emotional distress = Distress Thermometer > or = to 4 (n=74) *Attention Control* = 9 contacts by research assistant, supported by medical social worker (no data for patient contact with social worker) (n = 75) <u>Cancer-specific quality of life (QOL) tools</u>: a) Center for Epidemiological Studies-Depression Scale (CES-D) (total score range 0 to 60; score > or = to16 indicates impairment) b) Ambiguity subscale of the Mishel 'Uncertainty in Illness' Scale (MUIS) (scores range 13 to 65; higher scores, more uncertainty) c) Symptom Distress Scale (SDS) (rated from 1–5; "1" indicates absence/low symptoms; "5" = high symptom severity)	Cancer-specific QOL measured at baseline (24– 48 hours after surgery) 1, 3, and 6 months post-surgery Adjusted QOL baseline scores were included as covariates in **3 types of mixed effect regression models,** built to estimate **'rates of change'** in different QOL measures over time: **(1) Oncology NP without PSYNP** Effect Estimate (EE) <u>Uncertainty of Illness (MUIS)</u> EE = - 0.04847 ± se 0.01394, p = 0.0006 Rate of reduction in MUIS score was significantly greater for intervention vs control <u>CES-Depression (CES-D)</u> EE = 0.06566 ± se 0.02190, p = 0.0030 <u>Symptom Distress Scale (SDS)</u> EE = 0.05092 ± se 0.01638, p = 0.0021 Rate of change in CES-D, and SDS was significantly greater for control vs intervention **(2) Oncology NP with PSYNP** Effect Estimate (EE) <u>Uncertainty of Illness (MUIS)</u> EE = - 0.03917 ± se 0.00915, p < 0.0001 Rate of reduction in MUIS score was significantly greater for intervention vs control	**(2) Oncology NP with PSYNP** continued <u>CES-Depression (CES-D)</u> EE = 0.03594 ± se 0.01213, p = 0.0033 Rate of change in CES-D score was significantly greater for control vs intervention <u>Symptom Distress Scale (SDS)</u> Poor model fit – no EE data **3) PSYNP without Oncology NP** Effect Estimate (EE) The PSYNP component significantly increased the rate of improvement over time in all QOL measures except for the CES-D <u>Uncertainty of Illness (MUIS)</u> EE = - 0.04978 ± se 0.02094, p = 0.0181 <u>Symptom Distress Scale (SDS)</u> EE = - 0.1164 ± se 0.01284, p < 0.0001 <u>CES-Depression (CES-D)</u> EE = 0.01662 ± se 0.03549, p = 0.6400 non-significant rate of change	Standardized tools reliable and valid: Center for Epidemiological Studies-Depression Scale (CES-D); Mishel 'Uncertainty in Illness' Scale (MUIS); and Symptom Distress Scale (SDS) Baseline measures were obtained prior to randomization, with significant differences found in the CES-D and MUIS baseline scores; lower baseline QOL overall in the NP intervention group Baseline QOL scores were adjusted for model testing, with final covariates including age, marital status, number of comorbidities, disease status (recurrence or not), and education level Cancer care that addresses both physical and emotional QOL in synchrony, may contribute to enhanced rate of improvement in QOL as per study

Williams, 2005 [60] IPT ^^ Primary Health Care (PHC) 3746 PHC patients aged 40 years and over living in private households, with incontinence several times per month or more, or several times a year, and reported impact of symptoms on quality of life. Six month intervention period, at patients' homes in Leicestershire and Rutland, England	*Intervention* = continence service provided by NPs (n = 2958) *Control* = existing usual primary care including GP and continence advisory services (n =788) 4:1 ratio was deemed necessary to ensure sufficient intervention data for evaluation of detrusor muscle (wall of bladder) over-activity and urodynamic stress incontinence (involuntary leakage of urine with increased intra-abdominal pressure in the absence of detrusor contraction)	*<u>Improvement in one or more symptoms , cure (no symptoms)</u> at 3 months NP 60% (1417/ 2378 responders) Control 48% (281/584 responders) 12% difference (95% CI 7 to 16) p < 0.001 <u>6 months</u> NP 62% (1369/2201 responders) Control 52% (277/536 responders) 10% difference (95% CI 6 to 15) p < 0.001	<u>Cure</u> = 0 symptoms <u>3 months</u> NP 25% (591/2378) Control 15% (88/584) 10% difference (95% CI 6 to 13) p < 0.001 <u>6 months</u> NP 28% (624/ 2201) Control 19% (104/536) 9% difference (95% CI, 5 to 13) p < 0.001 <u>Number of symptoms alleviated</u> At 3 and 6 month time points, the percentage of responders reporting each of all four symptoms /events were statistically significantly less in the intervention group than control, with the exception of one borderline result at p = 0.066. Differences between groups ranged from 11%, p <0.001 to 4%, p = 0.066	Endpoint assessment based on the Leicester Urinary Symptom Questionnaire (developed for this study. Shaw (2004) reported high internal consistency, with measures of construct validity as hypothesised, and test-retest / inter-rater reliability moderate to excellent Significant improvements in the 'number of symptoms improved,' including 'cure' (no symptoms), were found for patients using the NP service, as per study

#Williams, 2011 [81] **Post Hoc Analysis** Six year follow-up to Williams (2005) IPT ^^ Primary Health Care (PHC) *November 2016* £ 1.00 Great Britain = $1.67 Canadian £ 0.60 Great Britain = $1.00 Canadian	*Intervention* = continence service provided by NPs (n = 2958) *Control* = existing usual primary care including GP and continence advisory services (n =788) The NP continence service was designed for the trial, and funded only for the trial's duration, not for the interim period of 6 years (expiry date unknown)	<u>Long term improvement in one or more symptoms at 6 years</u> NP 72%, 1530/ 2045 Control 67%, 380/567 Difference 5% (95% CI 0.6 to 9) p = 0.02	<u>Cure (no symptoms) at 6 years</u> NP 31%, 643/2069 Control 27%, 156/571 Difference 4% (95% CI -0.4 to 8) p = 0.08	Service was specifically designed for study purposes Funding of the continence service was not possible following completion of the research program, post original trial
Mitchell, 2009 [54] IPT ^^ Outpatient / Specialized Referral 101 patients within 4 months of an ischemic stroke, verified by computerized tomography (CT) scan or magnetic resonance imaging (MRI) and diagnosis of clinical depression; eight week intervention within a 24 month study period, at outpatient clinics, including rehabilitation facilities, or private homes, U.S.	*Intervention* = Brief psycho-social/behavioural intervention: nine in-person sessions with NP over 8 weeks + usual care, including antidepressant medication (n=48) *Control* = usual care (UC) by stroke care provider including antidepressant medication (n=53)	*<u>Mean change Hamilton Rating Scale for Depression (HRSD)</u> at 12 months NP -9.2 (5.7) 44/48 patients UC: -6.2 (6.4) 48/53 patients Difference of -2.9 (CI -5.4 to -0.4), p = 0.023 <u>Percent of patients in remission (HRSD < or = to 9)</u> at 9 weeks NP 47% 45/48 patients UC 19% 53/53 patients Difference 28 % OR = 4.8 (CI 1.8 to 12.9) p = 0.001 <u>Remission at 21weeks</u> NP 46% (46/48 patients) UC 22% (50/53 patients) Difference 24% OR = 3.4 (CI 1.3 to 8.7) p = 0.008	<u>Remission at 12 months</u> NP 48% (44/48 patients) UC 27% (48/53 patients) Difference 21% OR = 2.7 (CI 1.1 to 6.6) p = 0.031 <u>Remission at 24 months</u> NP 65% (44/48 patients) UC 46% (48/53 patients) Difference 19% OR = 2.3 (CI 0.8 to 6.7) p = 0.130 Measures of <u>overall stroke impact, limitations in physical function, social participation</u> at 12 months, were non-significant	Endpoint assessment based on the reliable and valid HRSD (Hamilton Rating Scale for Depression), the Barthel Index for measuring physical activity, and the Stroke Impact Scale Analysis per protocol, with 9% (9/101) of patients lost to 1 year follow-up Family participation / patient support was not a consistent factor between groups

Mertens, 2014 [68] IPT ^^ Primary Health Care (PHC) 403 PHC clinic patients 18–24 years, screened for high-risk alcohol and / or drug use; study period three months at a large PHC clinic, South Africa	*Intervention* = Single session of Brief Motivational Interviewing (average session 10 minutes) delivered by NP + referral list of resources (n=206) *Control* = minimally enhanced usual care including referral list of resources (n=197)	*****<u>Mean percent reduction in ASSIST scores for alcohol use</u> at 3 months ASSIST = Alcohol, Smoking and Substance Involvement Screening Test NP 38.3 % Control 20.9% p = 0.0293	<u>Mean percent reduction in ASSIST scores for cannabis use</u> at 3 months NP 28.3% Control 9.8% p = 0.1119 <u>Mean percent reduction in ASSIST scores for methamphetamine use at use</u> at 3 months NP 57.2% Control 76.9% p = 0.2264	Endpoint assessment used the ASSIST tool: Six questions / each substance reported, scored for low risk use or medium/ high risk use. The World Health Organization developed and validated this tool in PHC clinics in high, middle-and low-income countries including South Africa Raw data in Table 2 incomplete: no fraction of patients comprising percentages was reported. Attrition 40/403 or 10%
Tranmer, 2004 [46] IPT ^^ Outpatient / Specialized Referral 200 cardiac surgery outpatients discharged from first cardiac surgery with no stay at Intensive Care Unit (ICU). Five week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge, eastern Canada	*Intervention* = Usual Care + NP initiated phone contacts for patients in 1st 5 weeks following hospital discharge (n= 102) *Control* = Usual Care (UC) including education booklet, home-care follow-up as necessary, and NP contact information, with instruction to call with questions or concerns (n= 98)	<u>Mean number (SD) post-operative symptoms</u> at week 5 <u>Physical</u> symptoms NP 3.5 (2.6) UC 3.8 (2.9) p = 0.39 <u>Psychological</u> symptoms NP 2.4 (2.1) UC 2.3 (2.2) p = 0.64	<u>Cardiac</u> symptoms NP 1.5 (1.1) UC 1.7 (1.1) p = 0.29 <u>Total</u> symptoms NP 8.1 (5.0) UC 8.5 (5.5) p = 0.74	The Memorial Symptom Assessment Scale's (MSAS) reliability and validity was established in cancer patients, not cardiac patients, although cardiac symptoms were added to this study's measurement scale, including: palpitations, shortness of breath, and leg swelling

Sawatsky, 2013 [48] IPT ^^ Outpatient / Specialized Referral 204 postoperative cardiac surgery outpatients following first time coronary artery bypass graft (CABG) surgery. Six week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge. Patients with significant issues/concerns were seen at an NP Follow-up (NPFU) Clinic, western Canada	*Intervention* = = Usual Care + NP phone contact at 2-3 days post discharge for needs assessment, with recommendations to follow-up with primary care provider, cardiac surgeon, receive additional phone contact from NP, go to NPFU clinic, or to local ED (n= 97) *Control* = Usual Care (UC), including advice to make primary care provider appointment within 1 week; return visit to cardiac surgeon was scheduled for all patients at 6 weeks (n=107)	<u>Mean (SD) summary symptom-score</u> (number and frequency of symptoms) 2 weeks NP 45.2 (10.2) UC 50.4 (12.6) Difference 5.2 p = 0.002	6 weeks NP 41.2 (11.1) UC 43.2 (11.1) Difference 2.0 p = 0.23 Palpitations and leg pain were reported with less frequency in NP group versus UC at 6 weeks post-discharge p < 0.05 no individual data shown	Endpoint assessment based on the 'Symptom Inventory,' a 20-item questionnaire developed to measure specific symptoms related to cardiac surgery recovery Chronbach's alpha = 0.80 (Artinian & Duggan 1993) Disruption of randomized sample: once intervention was established, several control patients were pulled from trial, deemed too ill for the study (Sawatsky, 2013, p. 2085)

Krichbaum, 2007 [64] IPT ^^ Outpatient / Specialized Referral **Pilot study** 33 hip fracture surgery outpatients at least 65 years Six month intervention in a 12 month study period; mobile NP followed the patient to all discharge locations, including subacute care facilities, long term care facilities, rehabilitation agencies, and private homes, U.S.	*Intervention* = usual care + post-acute care coordination by gerontologic NP (n=17) *Control* = usual care according to hospital and individual surgeon's protocols for the post-acute care period (n=16)	Mean (SD) symptoms at 12 months <u>all non-significant</u> <u>Self-rated health</u> (Global Health self-ratings - higher scores better) NP 4.1 (0.95) Control 4.0 (0.71) Depression (Geriatric Depression Scale - higher scores worse) NP 2.2 (2.4) Control 1.7 (1.7)	<u>Activities of daily living</u> (ADLs: higher scores worse) 1. Mobility NP 1.42 (0.48) Control 1.24 (0.34) 2. Personal care NP 1.22 (0.32) Control 1.41 (0.53) <u>Instrumental ADLs</u> (IADLs: (higher scores worse) 1. Home chores NP 1.44 (0.19) Control 1.48 (0.51) 2. Social NP1.54 (0.61) Control 1.39 (0.49)	Endpoint assessment based on Global Health self-ratings, the Geriatric Depression Scale, and the Functional Status Index High attrition (30%; 10/33) Four patients withdrew: 3 control and 1 intervention Six patients died, three from each group: 3 to cancer, 1 from myocardial infarction, 1 from stroke, and 1 from post-operative complications
Schuttelaar, 2010 RS ^ Outpatient / Specialized Referral 160 patients < 16 years: 80 patients aged < or = to 4 years and 80 patients aged 4–16 years, all new referrals from GPs or pediatricians with a diagnosis of atopic dermatitis (eczema); 1 year study at an outpatient clinic, Netherlands	*Intervention* = NP-led care (n = 81) Age < or = to 4 years (n = 40) Age 4-16 years (n = 41) *Control* = conventional care by dermatologist (n = 79) Age < or = to 4 years (n = 40) Age 4-16 years (n = 39)	*<u>Eczema-specific Quality of Life</u> (higher scores poorer quality of life) <u>Mean (SD) Infants' Dermatitis Quality of Life Index</u> at 12 months NP 5.7 (5.4) Dermatologist 5.6 (3.9) p= 0.26 <u>Mean (SD) Children's Dermatology Life Quality Index</u> at 12 months NP 4.9 (3.5) Dermatologist 5.6 (4.2) p= 0.55	<u>Mean (SD) in eczema severity</u> at 12 months NP 13.2 (16.6) (73/81) Dermatologist 13.1 (17.1) (70/79) <u>Between-groups difference</u> reported as 0.2 (95% CI 5.4 to 5.7), p = 0.9	Endpoint assessment used the 'SCORing Atopic Dermatitis' (SCORAD) index Intervention treatment primarily carried out by one NP in single dermatology outpatient clinic

Pioro, 2001 [71] RS ^ Acute Inpatient 381 heterogeneous internal medicine inpatients 18–69 years, admitted for gastrointestinal, pulmonary, infectious, metabolic/ substance abuse, neurological, cardiovascular and "other" acute illnesses; study duration from hospital admission to 6 weeks post-discharge at single center teaching hospital, U.S.	*Intervention* = NP-based care (n=193) *Control*=House-staff care (n=188)	Functional Status at 6 weeks following discharge (no standard deviations accompanied report of mean values) Mean change in activities of daily living NP 0.1 (76/193) House-staff 0.2 (86/188) Difference - 0.1 (95% CI -0.5, 0.3) $p < 0.10$ Mean change in independent activities of daily living NP 1.4 (76/193) House-staff 2.1 (86/188) Difference - 0.7 (95% CI -1.4, 0.1) $0.05 < p < 0.10$	Mean Decrease in Symptom Severity at 6 weeks following discharge NP 4.0 (76/193) House-staff 4.7 (86/188) Difference -0.7 (95% CI -2.6, 1.2) $p > 0.1$ Patient Assessment of Care at 6 weeks following discharge (mean overall rating:0–100) NP 84.7 (76/193) House-staff 80.7 (86/188) Difference 4.0 (95% CI -3.0, 11.0) $p > 0.1$	Outdated references regarding tools used for functional status data, collected via patient interview: Katz *et al*. 1963; Lawton & Brody 1969; higher scores worse Although interviews were carried out by a trained research assistant, attrition by 6 weeks was 57%, with only 43% of patients completing interview data at 6 weeks. Reasons included failure to obtain patient consent, patient too ill, patient unable to speak English, failure to complete the mental status screen, and 'other.'

McClellan, 2012 [63] RS ^ Acute Emergency Department Equivalence Trial - designed to show that two interventions do not differ in either direction ('zone of indifference' regarding inferiority or superiority / 'equivalence margin') by more than a pre-specified unimportant or insignificant amount (i.e., a two-sided test)[85] 372 patients with peripheral soft tissue injury, older than 16 years, eligible for management by any of 3 professionals: Emergency NP (ENP), Extended Scope Physiotherapist (ESP), Emergency Department (ED) Doctor. Eight week study period at a single inner city ED, England	*Intervention* = patient management from arrival to discharge by ENP or ESP ENP (n = 123) ESP (n = 126) *Contro*l = routine ED doctor care from doctors of all grades (n =123)	*<u>Percentage return to normal function</u> at 8 weeks MCID (minimal clinically important difference) of 9 <u>95% CIs</u> Dr 45 to 80 (63.3%) (68/123) ESP 52.5 to 65.0 (59.2%) (72/126) ENP 55.0 to 66.3 (60.0%) (73/123)	<u>Preference-based health utility scores</u> at 8 weeks for percentage recovery to preinjury levels MCID of 5 using the Short Form-6D (SF-6D) <u>95% CIs</u> Dr 86.2-105.8 (92.2%) (68/123) ESP 93.2-100 (94.3%) (72/126) ENP 87.8 to 99.5 (92.2%) (73/123) All 3 groups were reported clinically equivalent	<u>Equivalence margin</u> of five was calculated using the smallest MCID from all outcome measures High reliability & validity to the 'Disability of the Arm, Shoulder and Hand' (DASH) score and the 'Lower Extremity Functional Score' (LEFS) for calculation of the percentage return to normal function; the MCIDs for these outcomes facilitated assessment of equivalence Main analysis was by intention-to-treat; a per-protocol (PP) analysis was also undertaken (McClellan, 2012, p.3) although no PP data is shown
Cooper, 2002 [62] RS ^ Acute Emergency Department	*Intervention* = ENP-led care (n = 102) *Control* = Senior House Officer	<u>Follow-up on recovery</u> at one-month ENP n = 63 patients SHO n = 65 patients Non-significant differences between groups included:	Questionnaire yielded a 64% response rate, following postal reminder	Limitations inherent to all self-completion questionnaires: 1) refusal to complete/return the questionnaire; bias if non-responders

204 patients over 16 years, with minor injury that fell within the ENP (emergency NP) protocol, at a single Accident and Emergency (A & E) Department 2 month study duration, Scotland	(SHO)-led care (n = 102)	<u>Level of symptoms</u> Swelling p = 0.92 Stiffness p = 0.80 Time to fully recover p = 0.96 <u>Level of activity</u> Looking after themselves p = 0.58 Ability to go to work / school p = 0.40 Sleep pattern p = 0.87 Productivity / time off work p = 0.14 No individual data shown		differ from responders 2) Patients may also ask other people to assist in completing the questionnaire, or even complete it on their behalf, prejudicing the sample 3)Lack of ability to read (low literacy levels / illiteracy in patients) may contribute to nonresponse
Nathan, 2006 [49] RS ^ Outpatient / Specialized Referral 154 outpatients > 16 years of age recently discharged from hospital related to acute asthma Six month study duration post-discharge, from hospital outpatient clinic, England	*Intervention* = NP care (n= 78) *Control* = Respirologist care (n=76)	<u>Mean (SD) percentage drop in peak flow</u> at 6 months NP 3.92% (12.4) Control 2.53% (11.5) Difference 1.39% (95% CI – 3.84 to 6.63) p = 0.122 <u>St. George's Respiratory Questionnaire</u> (SGRQ) higher score indicates greater limitations <u>Mean (SD) percentage reduction in SGRQ score</u> at 6 months NP 3.94% (14.34) (49/78) Control 5.02% (16.43) (52/76) Difference = 1.08% (95% CI – 5.0 to 7.2) p = 0.727	<u>Airways Questionnaire 20</u> (AQ20) high score indicates poor quality of life <u>Mean (SD) change in AQ20 score at 6 months</u> NP 0.47 (3.73) reduction (49/70) Control 0.31 (3.53) increase (52/66) Between-groups difference of 0.78 (95% CI – 0.64 to 2.19) p = 0.285	Data collected by an independent research assistant who was unaware of the group to which the patient was allocated Endpoint assessment of peak flow based on clinic measures at 2 weeks and 6 months SGRQ and AQ20 both reliable and valid

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT) #Post Hoc Analysis

Table I-4 Drug Utilization Endpoint-Outcomes

Statistically significant differences in 3 IPT^^ studies, 1 RS^ study

Inhaled Corticosteroids in *Respiratory Disease Patients*, Primary Health Care IPT
Self-reported NSAID Reduction in *Patients with Chronic Non-malignant, Non-inflammatory Musculoskeletal Pain*, Primary Health Care IPT
Target Use of Beta-Blocker Medication in *Chronic Heart Failure Patients*, Outpatient IPT (pilot study)
Medication Administration for *Soft Tissue Injury Emergency Department Patients*, Acute RS

No statistically significant differences in 2 IPT^^ studies, 2 RS^ studies (positive results)

Compliance to Lipid-Lowering Medication in *Coronary Heart Disease Patients*, Outpatient IPT
Self-Reported Drug Utilization in *Cardiovascular Disease Patients*, Outpatient IPT
Medication Adjustment for Improved Symptom Control in *Rheumatoid Arthritis Patients*, Outpatient RS
Numbers of Prescriptions to *Patients with 'Common Complaints'* Primary Health Care RS

Author, Year **RS^ / IPT^^** **Setting** **Study Population, Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)		**Quality of Endpoint Assessment / Comments**
Fairall, 2005 [8] Cluster RCT unit of random allocation = clinic IPT ^^ Primary Health Care (PHC) Priority Respiratory Diseases: LRTI (Lower Respiratory Tract Infection), URTI (Upper Respiratory Tract Infection), asthma, tuberculosis (TB), HIV, and Chronic Obstructive Pulmonary Disease (COPD)	*Intervention* = PALSA (Practical Approach to Lung Health in South Africa) an educational outreach program of expanded prescribing provisions with locally tailored guidelines, implemented by NPs 20 clinics randomized to outreach intervention (1000/1999	*Prescriptions at 3 months Inhaled Corticosteroids for asthma Outreach 13.7% (137/1000) Control 7.7% (77/999) OR = 1.90 (95% CI = 1.14 to 3.18) p = 0.006 ICC = 0.019 Antibiotics for URTI & LRTI Outreach 39.7% (397/1000)	Prophylactic cotrimoxazole prescriptions for HIV patients with a diagnosis of tuberculosis Outreach 7.8%, (13/167) Control 7.5% (11/147) Difference= 0.3% Non-significant Smoking cessation Outreach 12.2%, (20/164)	Endpoint assessment by fieldworkers blinded to the intervention, was based on data collection from patient-held records, together with records of dispensed drugs Patients and fieldworkers were blind to the intervention status of each clinic, while NPs allocated to the intervention arm could not be blinded for

40 primary health care (PHC) clinics staffed by NPs were randomized, including 1,999 patients with cough or difficult breathing on presentation, or within past 6 months Three month study period, South Africa	patients) *Control* = Usual NP Care, with no new training in educational outreach program 20 clinics randomized to usual care (999/1999 patients)	Control 39.4% (394/999) OR = 1.01 (95% CI = 0.74 to 1.38) p = 0.95 ICC = 0.042	Control 10.4%, (20/193) Difference=1.8% Non-significant	obvious reasons Low number of educational contacts, reportedly due to difficulties accommodating visits in small town / rural PHC clinics
Jones, 2002 [66] IPT ^^ Primary Health Care (PHC) 222 PHC patients from 5 general practices with computerized prescribing systems. Patients were 18 years or older, with non-malignant, non-inflammatory musculoskeletal pain and oral non-steroidal anti-inflammatory drug (NSAID) prescriptions covering 6 or more weeks of the last 12 months <u>GALS screen</u> (Gait, Arms, Legs & Spine) assessment to detect locomotor abnormalities related to musculoskeletal pain Six month study, with all patients examined at their general practice or their homes, England	*'Active Intervention'* = NP assessment, patient-tailored educational package, with request that patients withdraw their NSAIDs and use appropriate alternative drug and non-drug therapies (e.g. strategies on weight reduction, aerobic exercise, use of local heat and cold, back and neck care, footwear, massage, and relaxation techniques) + Usual GP Care (n =110) *'Control Intervention'* = same single NP provided assessment and basic education regarding NSAID use, reinforced with leaflet + Usual GP Care (n =112)	*<u>Self-reported reduction in oral NSAID dose</u> by 50% or less, at 6 months <u>Active NP Intervention</u> 38 % (42/110) <u>Control</u> 13% (14/112) Difference 25% p < 0.0001		Self-reported drug utilization, alongside computer records of prescribing data Element of 'social desirability' where active intervention provided advice for reduction of NSAID use; potential bias in same single NP for both intervention and control groups

McClellan, 2012 [63] RS ^ Equivalence Trial - designed to show that two interventions do not differ in either direction ('zone of indifference' regarding inferiority or superiority; the 'equivalence margin') by more than a pre-specified unimportant or insignificant amount (i.e., a two-sided test)[85] Acute Emergency Department 372 patients with peripheral soft tissue injury, older than 16 years eligible for management by any of three professionals: Emergency NP (ENP), Extended Scope Physiotherapist (ESP), Emergency Department (ED) Doctor Eight week study period at a single inner city ED, England	*Intervention* = patient management from arrival to discharge by ENP or ESP ENP (n = 123) ESP (n = 126) *Contro*l = routine ED doctor care from doctors of all grades (n =123)	<u>Medication administration</u> <u>ESPs</u> 3.6% patients <u>NPs</u> 23.2% patients <u>Doctors</u> 42.2% patients Differences between groups p < 0.001	NPs and ESPs were reported to be clinically equivalent to routine care provided by doctors, despite significant differences in prescribing patterns	<u>Equivalence margin</u> was a difference of five calculated using the smallest minimal clinically important difference from all outcome measures Limited endpoint assessment related to no disclosure regarding how / by whom medication administration was measured. Incomplete raw data with no numbers for fractions of groups comprising reported percentages. Although main analysis was by intention-to-treat, a per-protocol (PP) analysis was also undertaken, though no PP data is shown
Ansari, 2003 [45] **Pilot RCT** Two levels of individual randomization IPT ^^ Outpatient / Specialized Referral 169 outpatients meeting Framingham criteria for Chronic Heart Failure (CHF) were individually randomized into 3 groups 74 providers (internal	*Notification Intervention* Beta-blocker advocacy Internists 10 Cardiologists 2 NPs 3 (n = 64 patients) *NP Facilitator Intervention* Initiation, titration, and stabilization of CHF patients on beta-blockers	*<u>Beta blocker use in CHF outpatients</u> <u>Patients either initiated or up-titrated on beta-blockers</u> Notification 16% (10/64) NP facilitator 67% (36/54) Control 27% (14/51) p < 0.001	<u>Mean length of time from initiation to target dose</u> Notification 9.3 months NP facilitator 5.9 months Control 8.5 months p < 0.001	Endpoint assessment based on an independent research assistant assessing the use of beta blocker therapy, by reviewing pharmacy records and computerized progress notes

medicine doctors, cardiologists and NPs) were also individually randomized into 3 groups, to decrease the likelihood of contamination, i.e. patients receiving care from their regular providers; Median follow-up period = 12 months, at a single academically affiliated medical center, U.S.	Internists 19 Cardiologists 3 NPs 3 (n=54 patients) *Control* Provider education regarding beta blocker guidelines Internists 16 Cardiologists 4 NPs 4 (n=51 patients)	<u>Target doses of beta-blocker medication</u> Notification 2% (1/64) NP facilitator 43% (23/54) Control 10% (5/51) $p < 0.001$		
Allen, 2002 [44] IPT ^^ Outpatient / Specialized Referral 228 coronary heart disease (CHD) outpatients who received coronary artery bypass grafting (CABG) surgery or percutaneous coronary intervention (angioplasty), with hypercholesterolemia (low density lipoprotein cholesterol level > 2.59 mmol/L or total cholesterol level > 5.18 mmol/L) Intervention for one year post-discharge, at outpatient clinic of large tertiary hospital, U.S.	*Intervention* = NP case management (individualized lifestyle and pharmacologic intervention) + Enhanced Usual Care (n = 115) *Control* = Enhanced Usual Care (EUC) from primary providers and/or cardiologists including full lipid profiles sent to patients and their physicians at 4 weeks, 6 and 12 months after discharge, including goals for levels of lipoproteins, diet and physical activity (n =113)	<u>Medication compliance to lipid-lowering drugs</u> at one year NP 87% (100/115) EUC 79% (89/113) Difference 8% $p = 0.10$		Evaluation of medication use at admission and discharge based on admission history / physical examination, hospital records, and discharge summaries Among patients on pharmacotherapy, 97% in both groups were taking a single statin agent: 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor

Goessens, 2006 [47] IPT ^^ Outpatient / Specialized Referral <u>Cardiovascular disease (CVD)</u> Peripheral arterial disease Abdominal aortic aneurysm Cerebrovascular disease Coronary heart disease 236 CVD outpatients with two or more modifiable risk factors: smoking, hypertension, dyslipidemia, diabetes, obesity, hyperhomocysteinemia. Intervention for one year after randomization at a risk-factor management clinic in the University Medical Center Utrecht, Netherlands	*Intervention* = NP at risk factor management clinic + usual care (n=119) *Control* = usual care (UC) by GP and treating vascular specialist (n=117) At the time of the trial, an NP in the Netherlands was not formally allowed to prescribe; instead, a study physician prescribed or changed medication for patients in the trial	<u>Self-reported Drug Utilization</u> at mean follow-up of 14 months (range 10 -22 months) <u>Lipid-lowering drugs</u> NP 89% (80/90) UC 73% (55/75) Difference 16% <u>Glucose-lowering agents</u> NP 19% (17/90) UC 16% (12/75) Difference 3% <u>Blood pressure lowering agents</u> NP 77% (69/90) UC 69% (52/75) Difference 8%	<u>Angiotensin converting enzyme inhibitors /angiotensin II antagonists</u> NP 76% (57/90) UC 53% (40/75) Difference 23% <u>Folic acid</u> NP 61% (55/90) UC 28% (21/75) Difference 33% <u>Antiplatelet agents</u> NP 90% (81/90) UC 91% (68/75) Difference – 1%	Self-reported drug utilization not able to be cross-checked with formal pharmacy records Patients were randomized before informed consent was obtained, according to the Zelen design; treatment consent is always sought before actual intervention, Torgerson & Roland (1998) <u>Attrition</u> 31% (71/236) 61 patients gave no informed consent post randomization: 24 intervention and 37 control. Another 10 patients did not complete study: 4 deaths, 1 patient moved, and 1 patient developed co-morbidity
Hill, 2003 [55] RS ^ Outpatient / Specialized Referral 80 Rheumatoid Arthritis (RA) patients 18 years or older, to rheumatology clinic on at least three previous occasions. Study period 12 months, at a traditional rheumatology outpatient clinic managed by junior hospital doctors (JHDs) within a large teaching hospital, England	*Intervention* = rheumatology NP (RNP) care (n = 39) *Control* = junior hospital doctor (JHD) care (n = 41)	<u>Changes to medications for symptom control</u> NP 24% (56/234) JHD 22% (50/226) Difference 2%, Non-significant	<u>Numbers of prescriptions</u> for intra-articular / intramuscular corticosteroid injections NP 15% consults (36/234) JHD 13% consults (29/226) Difference 2% Non-significant	Drug utilization data of limited quality, related to no disclosure regarding how or by whom all medication changes / administration were noted Per protocol, actual treatment analysis

Dierick-van Daele, 2009 [67] RS ^ Primary Health Care (PHC) 1,591 primary health care patients from 15 general practices. Study patients were 16 years and older, with common complaints regarding respiratory/ throat, ear/nose musculoskeletal/skin injuries, urinary/ gynaecological and geriatric problems. 2 week intervention within a study duration of 6 months; patients who attended a general practice on a day when the NP was present were invited to participate in the trial, Netherlands	*Intervention* = patient care from newly graduated NPs with Master Degree of Advanced Nursing Practice, experience ranging from 1 to 5 years; 12 NPs (n = 817) *Control* = patient care from GP with an average of 16 years' experience; 50 GPs (n = 684) Study practices were compared to external reference practices where 17 GPs worked in 5 general practices without the involvement of NPs	<u>Numbers of prescriptions given</u> <u>One prescription</u> NP 55.0% (411/747) GP 54.2% (352/650) Difference 0.8% p = 0.75	<u>Two prescriptions</u> NP 16.9% (126/747) GP 19.5 % (127/650) Difference 2.6% p = 0.20 <u>Three or more prescriptions</u> NP 8.8% (66/747) GP 7.8% (51/650) Difference 1.0% p = 0.51	Prescription data were extracted from the clinics' computer systems In this study from the Netherlands, the NP had no full authority to prescribe medications. GPs therefore validated NPs' prescriptions, resulting in a potentially spurious endpoint of comparison

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT) #Post Hoc Analysis

Table I-5 Resource Utilization / Cost Endpoint-Outcomes: Acute Inpatient

Statistically significant difference in 1 RS^ study

Patient Wait Time in *Minor Injury Emergency Department Patients,* Acute RS

No statistically significant differences in 2 RS^^ studies (positive results)

Mean Length of Hospital Stay, Number of Consultations to other Services, Total Hospital Charges, Total Ancillary Charges in *Internal Medicine Inpatients*, Acute RS
Mean Cost / Hour Patient Care, Unit 'Cost / Patient / Hour' (salary / productivity), Average Number Patients Treated / Hour, Mean Direct Cost / Hour Patient Care, Mean Indirect Cost / Hour Patient Care, Number Patient Days Off Work at 8 weeks in *Soft Tissue Injury Emergency Department* Patients, Acute RS (post hoc analysis)

Author, Year **RS^ / IPT^^** **Setting** **Study Population, Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)		**Quality of Endpoint Assessment / Comments**
Cooper, 2002 [62] RS ^ Acute Emergency Department 204 patients over 16 years, with minor injury that fell within the ENP (emergency NP) protocol, at a single Accident and Emergency (A & E) Department; 2 month study duration, Scotland	*Intervention* = ENP-led care (n = 102) *Control* = Senior House Officer (SHO)-led care (n = 102)	<u>Patient's average wait time</u> (minutes) ENP 48.6 SHO 70.1 95% CI 11.2–31.8 p < 0.001 <u>Total consult time</u> (minutes) ENP 30.0 SHO 24. 95% CI -1.3 - 11.5 p < 0.115 <u>Missed injuries</u> ENP 1, SHO 1 <u>Seeking advice from senior medical staff</u> when X-ray interpretation (ENPs were required to consult; SHOs were not) was excluded ENP 20.9% SHO 11.5% p < 0.21	<u>Numbers of X-rays requested</u> ENP 56.6%, SHO 47.5%, p = 0.2 <u>Referral to follow-up clinics</u> ENP 33.3 % SHO 27.5% p = 0.358 <u>Reasons for unplanned return</u> regarding 6/10 NP patients and 4/10 SHO patients: New injuries ENP 1, SHO 1 Concern about original injury ENP 2, SHO 1 Problems complying with treatment ENP 2, SHO 1 Problems with treatment ENP 1, SHO 1	Endpoint assessment regarding wait time and consult time data, based on the use of the 'Treatment Record' form for consultations and referrals Returns to the emergency department by study patients and missed injuries were tracked by the hospital computer system

Pioro, 2001 [71] RS ^ Acute Inpatient 381 heterogeneous internal medicine inpatients 18–69 years, admitted for gastrointestinal, pulmonary, infectious, metabolic/ substance abuse, neurological, cardiovascular and "other" acute illnesses; study duration from hospital admission to 6 weeks post-discharge at single center teaching hospital, U.S.	*Intervention* = NP-based care (n=193) *Control*=House-staff care (n=188)	*Mean length of hospital stay (days) NP 5.0 House-staff 5.3 Difference - 0.3 days 95% CI -1.2 - 0.6 p > 0.10 *Mean number of consultations to other services (e.g. respiratory therapy) NP 1.4 House-staff 1.4 Difference of 0.0 95% CI - 0.2 - 0.3 p > 0.10	*Mean total hospital charges, costs (U.S.$) NP $8854 House-staff $9426 Difference - $572 95% CI -$2704 - $1560 p > 0.10 *Mean total ancillary charges, costs (U.S.$) NP $4960 House-staff $5358 Difference of -$399 95% CI -$1820 - $1023 p > 0.10 *Feb. 17, 2017* $1.00 U.S = $1.31 Canadian $0.76 U.S. = $1.00 Canadian	Incomplete reporting of raw data in Table 2. No fraction of patients was provided for derivation of resource utilization data No designated societal costs were reported. Costs did not explicitly consider differences in NP and house-staff salaries, costs of the medical director, nor costs of providing off-hours coverage by residents
#McClellan, 2013 [86] Cost Minimization Evaluation **Post hoc Analysis** to McClellan (2012) RS ^ Acute Emergency Department 372 peripheral soft tissue injury patients older than 16 years, eligible for management by any of 3 professionals: Emergency NP (ENP), Extended Scope Physiotherapist (ESP), Emergency Department (ED) Doctor. Eight week study period at a	*Intervention* = patient management from arrival to discharge by ENP or ESP NP group (n = 123) ESP group (n =126) *Control* =Routine ED doctor care (n = 123)	Primary measures 1) Mean cost per hour of patient care Doctors £80.91 (CI £66.5 to £101.6) ESPs £89.71 (£CI 73.0 to £118.7) ENPs £109.81 (CI £83.0 to £142.1) (undiscounted values) 2) Mean unit 'cost per patient per hour,' dividing the salary cost of different professional groups by their productivity: number of patients treated /hour)	Secondary measures 1) Mean direct cost (e.g. crutches, medications) per hour of patient care Doctors £60.96 (CI £51.1 to £73.6) ESPs £52.48 (CI £44.7 to £63.9) ENPs £55.21 (CI £47.0 to £66.0) (undiscounted values) 2) Mean indirect cost to patient and society per hour of patient care (e.g. unplanned additional visits, travel/parking costs) Doctors £19.60 (CI £11.2 to £38.6) ESPs £39.56 (CI £25.6 to£ 59.0) ENPs £52.70 (CI £33.0 to £81.6) (undiscounted values)	Low quality measurement tool: accuracy of self-reported time spent with patients by each professional, time upon which cost calculations were based, was not verified Numbers used in calculations, including salary, were not disclosed Cost minimization evaluation is a controversial method for cost evaluation of equivalence trials: cost–minimization analysis is performed when

single inner city ED, England *Feb.17, 2017* £ 1.00 Great Britain = $1.62 Canadian £ 0.62 Great Britain = $1.00 Canadian		Doctors £54.93 (CI £37.9 to £73.0) ESPs £68.36 (CI £50.6 to £91.3) ENPs £86.47 (CI £62.2 to £122.5) (undiscounted values) <u>Cost of each professional</u> = salary + salary 'on costs' + overheads + capital over-heads + travel + contact times + non-London multiplier <u>Average number patients treated / hour</u> Doctors 4.4 ESPs 3 ENPs 3.6	Based on costs incurred within hospital-based secondary care alone, NPs were reported to be equivalent in cost to routine care while ESPs were reported as either equivalent or less expensive than routine care. Uncertainty in cost arose from ESPs and NPs potentially incurring greater indirect costs, associated with follow-up appointments and subsequent primary care visits. <u>Societal Costs included 95% CIs for numbers of days off work at 8 weeks</u> (MCID = 5 Table 3, **McClellan, 2012**, p. 7) Doctors (0.0 - 6.0 days) n = 68 ESPs (0.75 - 2.0 days) n = 72 ENPs (1.0 - 2.5 days) n = 73	the health effects of the alternatives are known or assumed to be equal. Only the costs need to be analysed, and the least costly alternative is the most efficient. However, few interventions are actually equally effective.[91] Although main analysis was by intention-to-treat, a per-protocol (PP) analysis was also undertaken, though no PP data is shown

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT) #Post Hoc Analysis

Table I-6 Resource Utilization / Cost Endpoint-Outcomes: Outpatient

Statistically significant differences in 2 RS^ studies and 3 IPT^^ studies

Clinic Attendance in *Acute Asthma Patients*, Outpatient RS
Total Annual Healthcare Costs per Patient (including Societal Costs) with *Pediatric Eczema*, Outpatient RS (post hoc analysis)
Primary Health Care and Outpatient Clinic Visits by *COPD Patients*, Outpatient IPT (pilot study)
Primary Health Care Visits by *Post-operative Women with Suspected Ovarian Cancer*, Outpatient IPT (post hoc analysis)
Physician Office Visits by *Older Adults Discharged Home*, Outpatient IPT (pilot study)

No statistically significant differences reported in 2 RS^ studies and 4 IPT^^ studies

Number Hospital Readmissions / Patient in *Acute Asthma Patients*, Outpatient RS
Lab tests, X-rays, primary health care visits, referrals *Rheumatoid Arthritis Patients*, Outpatient RS
Readmission to hospital, emergency department, specialist, primary care provider, home care visits by *Cardiac Surgery Patients*, Outpatient IPT
Visits with primary care provider / cardiologist, emergency department visits, readmission to hospital by *Coronary Artery Bypass Graft Patients*, Outpatient IPT
Reduction in low-density lipoprotein cholesterol in *Coronary Heart Disease Patients*, Outpatient IPT (post hoc analysis)
Inpatient days, specialist, outpatient clinic, and primary health care visits in *Type 2 Diabetes Patients*, Outpatient IPT

Author, Year **RS^ / IPT^^** **Setting** **Study Population, Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)		**Quality of Endpoint Assessment / Comments**
Nathan, 2006 [49] RS ^ Outpatient / Specialized Referral 154 outpatients > 16 years of age recently discharged from hospital related to acute asthma; 6 months study duration post-discharge,	*Intervention* = NP care (n= 78) *Control* = Respirologist care (n=76)	<u>Mean number hospital readmissions / patient</u> (data also noted in Appendix I-1 as '1st type of exacerbation') NP 0.07 (5 readmissions /68 patients)	<u>Mean number clinics not attended</u> RR = 0.90 95% CI 0.54 to 1.48 p = 0.70 No significant difference in the number of clinics not	Data collected by an independent research assistant unaware of the group to which the patient was allocated

hospital outpatient clinic, England		Respirologist 0.18 (12 readmissions /65 patients) Relative risk of readmission = 0.40 95% CI 0.14 to 1.12, p = 0.09 <u>Mean number clinics attended</u> NP 1.97 (130 clinics/66 patients) Respirologist 2.23 (147 clinics/66 patients) RR = 0.88 95% CI 0.70 to 1.12, p = 0.011 Patients attended fewer NP clinics than Respirologist clinics	attended; no individual data shown <u>Mean number clinics cancelled by patient</u> RR = 1.65 95% CI 1.30 to 2.08 p = 0.052 Patients in the NP group were more likely to cancel appointment; no individual data shown <u>Mean number of clinics cancelled by practitioner</u> NP 0.32 Respirologist 0.08 RR = 4.20 95% CI 1.6 to 11.0 p = 0.004 More clinics were cancelled by NP than by Respirologist	Clinic attendance data gathered from hospital information system
Berkhof, 2014 [50] IPT ^^ Outpatient / Specialized Referral **Pilot study** 100 chronic obstructive pulmonary disease (COPD, a progressive disease) outpatients > or = to 40 years, COPD GOLD stage > or = to 2 (Global initiative for staging Obstructive Lung Disease: 1 = mild; 4 = very severe) smoking history >10 pack-years; 2 year study at a large teaching hospital in Zwolle, Netherlands	*Intervention* = patient-initiated outpatient visits with pulmonary NP upon increase of symptoms (dyspnea, cough, sputum, hemoptysis, or thoracic pain); NP followed an 'on-demand protocol' that included consult with pulmonologist for urgent problems (n =49)	<u>Median (range) healthcare visits</u> at 2 years **Primary** healthcare GP visits Intervention 4 (0-32) Control 5 (0-20) p = 0.01 **Secondary** care visits 1) Outpatient Pulmonary NP Intervention 1 (0-14) Control 0 (0-4) p = 0.003	<u>Mean (SD) total healthcare provider costs</u> at 2 years Intervention €1803 (€2617) Control €2321 (€3967) Difference € -518 (CI - €1993, €788) <u>Mean (SD) total healthcare</u>	Limited quality measure: GPs and pharmacists were contacted to collect primary health care resource-use data on themselves, in terms of GP visits and exacerbations. Data for secondary

Feb. 17, 2017 €1.00 Euro = $1.53 Canadian €0.72 Euro = $1.00 Canadian	*Control*= usual care (UC) of traditional outpatient visits initiated by pulmonologist, to the pulmonologist or the pulmonary NP (n=51)	2) Outpatient Pulmonologist Intervention 3 (0-17) Control 3 (0-13) p = 0.82	insurance costs at 2 years Intervention €3994 (€4669) Control €4452 (€ 6100) Difference - €458 (CI - €2700, € 1652) Reductions in total costs were not significant; however this pilot study was not designed for cost analysis	hospital-based care was collected from hospital computer system, regarding visits to the pulmonologists, PNPs, and exacerbations Healthcare provider cost data from StatLine, electronic databank of Statistics, Netherlands; insurance cost data from "the Diagnosis Treatment Combination 2013" of study hospital
#McCorkle, 2011 [79] Healthcare Utilization **Post Hoc Analysis** to McCorkle (2009)[52] IPT ^^ Outpatient / Specialized Referral 149 post-surgical outpatients 21 years or older, with suspected primary diagnosis of ovarian cancer after abdominal surgery, prognosis of at least 6 months, and an order to initiate chemotherapy. Six month study duration, with patient contact made at private homes or by telephone, U.S.	*Intervention* = 18 contacts by an oncology NP, supported by psychiatric NP (PSYNP) consults (32/74 intervention patients) when warranted for high emotional distress = Distress Thermometer > or = to 4 (n=74) *Attention Control* = nine contacts by research assistant, supported by medical social worker (no data for patient contact with social worker) (n = 75)	* Resource Utilization at 6 months Mean (SD) inpatient admissions of ' > than 1 hospitalization' NP 2.43 (2.09) Control 1.62 (0.71) p = 0.4319 Mean (SD) Emergency Room (ER) visits: '> than 1 visit' NP 1.85 (1.14) Control 1.40 (0.74)	Mean (SD) Primary Health Care visits: '> than 1 visit' NP 2.75 (2.03) Control 3.59 (4.66) p =0.0003 The p values were evaluated with the Bonferroni correction (0.05/4 = 0.0124) The outcome of primary health care visits, with p = 0.0003 was the only significantly	Limited measurement of healthcare utilization: given self-reported visits had a 95% agreement with medical record review for 123 patients treated at the Cancer Center, this level of agreement was the rationale for including only self-reported data on an

	All 149 study patients received the Symptom Management Toolkit, an education manual with strategies to address 16 symptoms commonly experienced post-surgery with chemotherapy	p = 0.0852 Mean (SD) Oncology outpatient visits: ' > than1 visit' NP 9.19 (5.74) Control 8.27 (4.49) p = 0.5359	different result	additional 22 patients treated at affiliate hospitals, where self-reported data could not be cross-checked with hospital records Per protocol, actual treatment analysis
Enguidanos, 2012 [65] IPT ^^ Outpatient / Specialized Referral **Pilot study** 199 at-risk older adults discharged home from hospital without in-home care (e.g., home health or hospice) or without able/available caregivers; 6 month study set in a managed care medical center, or Health Maintenance Organization (HMO), with study patients recruited from hospital prior to discharge, U.S.	*Intervention* = Brief NP Transition, a 'bridge' of up to 3 home visits, 2 phone calls from primary health care NP, within 72 hours of discharge (n = 100) *Control* = standard medical care, including access to case management services (wait time 2-14 days) (n =99)	<u>Resource Utilization</u> at 6 months <u>Mean (SD) number of physician office visits</u> NP 9.94 (8.5) Control 11.72 (7.7) p = 0.036 <u>Mean (SD) number of emergency room visits</u> NP 0.50 (1.2) Control 0.99 (2.5) p =0.096	<u>Mean (SD) Hospital Days</u> NP 3.78 (8.8) Control 3.49 (6.5) p = 0.514 <u>Mean (SD) home health care days</u> NP 4.99 (8.7) Control 5.57 (9.3) p = 0.485 <u>Hospital re-admission rate</u> NP 40% Control 44.4% p = 0.526	Endpoint assessment: data collection from the Health Maintenance Organization 's (HMO) electronic medical record database at 6 months; did not include any medical service use that may have occurred outside of the HMO, accounting for ~ 3% of all service use Small sample size and attrition on follow-up surveys (~ a 65% response rate) limited detection of between-groups differences

#Schuttelaar, 2011 [78] Cost-Effectiveness Analysis (CEA) **Post Hoc Analysis** to Schuttelaar (2010) RS ^ Outpatient / Specialized Referral 160 patients < 16 years: 80 patients aged < or = to 4 years and 80 patients aged 4–16 years, all new referrals from GPs or pediatricians with a diagnosis of atopic dermatitis (eczema); 1 year study at an outpatient clinic, Netherlands *Feb. 17, 2017* €1.00 Euro = $1.53 Canadian €0.72 Euro = $1.00 Canadian	*Intervention* = NP led care (n = 81) Age < or = to 4 years (n = 40) Age 4-16 years (n = 41) *Control* = conventional care by dermatologist (n = 79) Age < or = to 4 years (n = 40) Age 4-16 years (n = 39)	<u>Mean (SD) annual healthcare costs per patient</u> (including family costs, and societal costs in other sectors) NP €981 (€ 1339) 76/81 patients Control €1409 (€ 2289) 71/79 patients Difference - €428 95% CI - € 910 to €197	For mild, moderate, severe eczema, mean total aggregate costs were consistently lower in the NP group	Data gathered from a clinical record form, medical record and electronic hospital information system, including a cost diary, with necessity of parent documenting on behalf of the infant / child; potential bias related to patient's cost diary
Sawatsky, 2013 [48] IPT ^^ Outpatient / Specialized Referral 204 postoperative cardiac surgery outpatients following first time coronary artery bypass graft (CABG) surgery Six week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge. Patients with significant issues/concerns were seen at an NP Follow-Up (NPFU) Clinic, western Canada	*Intervention* = Usual Care + NP phone contact at 2-3 days post discharge for 6 weeks, with recommendations to follow-up with primary care provider, cardiac surgeon, receive additional phone contact from NP, go to NPFU clinic, or to local ED (n= 97) *Control* = Usual Care (UC) primary care provider at 1 week; return visit to cardiac surgeon scheduled for all patients at 6 weeks (n=107)	<u>Health Care Resources Utilization at 6 weeks</u> <u>Total MD visits</u> NP 208 UC 210 Difference 2 visits <u>Total emergency department (ED) visits</u> NP 30 UC 37 Difference 7 visits	<u>Total hospitaliza-tions</u> NP 15 UC 19 Difference 4 hospitaliza-tions Reductions in total patient hospitalizations / total ED visits, while not statistically significant, may be clinically significant	Limited quality measurement tool: the 'Health Care Resources Utilization Questionnaire' was only pilot tested on 5 cardiac surgery patients. This tool was developed by the researchers to operation-alize the outcome of healthcare costs by eliciting the self-reported number of patient contacts/visits with their primary care

				provider and cardiologist, as well as ED visits and hospital admissions at the 2 and 6-week interviews. Costs were not reported
Tranmer, 2004 [46] IPT ^^ Outpatient / Specialized Referral 200 postoperative cardiac surgery outpatients discharged from first cardiac surgery with no stay at Intensive Care Unit (ICU). Five week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge, eastern Canada	*Intervention* = Usual Care + NP initiated phone contacts for patients in 1st 5 weeks following hospital discharge (n= 102) *Control* = Usual Care (UC) including education booklet, home-care follow-up as necessary, and NP contact information, with instruction to call with questions or concerns (n= 98)	<u>Self-reported health care contacts</u> at 5 weeks <u>At least 1 visit to the ER</u> NP 21 UC 15 p = 0.36 <u>Unexpected hospital admissions</u> NP 9 UC 8 p = 0.85 <u>Home care on discharge</u> NP 27 UC 26 p = 0.88	<u>Mean (SD) home care visits</u> NP 11.68 (9.4) UC 10.07 (8.0) p = 0.87 <u>Family physician</u> NP 88 UC 86 p = 0.86 <u>Specialist</u> NP 50 UC 51 p = 0.88	Resource use tracked through patient self-report, with no reference to any tool used, nor any reference to verification with hospital records
#Paez, 2006 [83] Cost-Effectiveness Analysis (CEA) **Post Hoc Analysis** to Allen (2002) IPT ^^ Outpatient / Specialized Referral 228 coronary heart disease (CHD) outpatients who received coronary artery bypass grafting (CABG) surgery or percutaneous coronary	*Intervention*= NP case management (individualized lifestyle and pharmacologic intervention) + Enhanced Usual Care (EUC) for 1 year post-discharge (n = 115) *Control* = Enhanced Usual Care (EUC) from primary providers &/or cardiologists including full lipid profiles sent to	<u>Total costs at 1 year</u> NP $1,573.31 EUC $1,182.81 Total incremental cost (NP - EUC) = $390.50 <u>Cost-effectiveness ratios</u> 1 year (U.S.$) Cost per mg/dL reduction in LDL cholesterol $26.03	Cost-effectiveness analysis (CEA) found the NP to be less cost-effective than anticipated Less expenditure of NP time was offset by more costly drugs used for patients as the study proceeded	Limited quality measurement: self-reported drug use at 6 and 12 months NP kept a daily log of time taken for each patient Without consideration of societal costs it may be noted that costs of NP management

intervention (angioplasty), with hypercholesterolemia (low density lipoprotein cholesterol level > 2.59 mmol/L or total cholesterol level > 5.18 mmol/L); intervention for one year post-discharge, at outpatient clinic of large tertiary hospital, U.S. *Feb. 17, 2017* $1.00 U.S = $1.31 Canadian $0.76 U.S. = $1.00 Canadian	patients and their physicians at 4 weeks, 6 and 12 months after discharge, including goals for levels of lipoproteins, diet and physical activity (n =113)	Cost per % reduction in LDL cholesterol $39.05	One year study did not allow for a comprehensive CEA that considers savings associated with prevention of cardiovascular events by assuming the societal perspective	are relatively nominal vs medical and disability-related costs associated with treating CV catastrophic events and living with the consequences
Ralston, 2009 [6] IPT ^^ Outpatient / Specialized Referral 83 Type II Diabetes Mellitus outpatients, 18 - 75 years with glycosylated hemoglobin (GHb) in prior year > or = to 7%; at least 2 clinic visits in prior year; 12 month intervention period, at the University of Washington General Internal Medicine Clinic (UW GIMC), a teaching clinic that provides care to 7, 707 patients, staffed by 25 faculty, 48 residents, and an NP, for case management of chronic disease patients, U.S. (Ralston, 2009, p. 234)	*Intervention* = NP coordination of Web-based care + usual care (n=42) *Control* = usual care (UC) from a physician who was board certified in internal medicine at the UW GIMC; all providers used the same electronic medical record (n=41)	<u>Mean (SD) change in total numbers of visits</u> at 12 months <u>Primary Health Care Clinic</u> NP 0.0 (2.9) UC -0.2 (2.8) Difference 0.2 p = 0.76 <u>Outpatient Clinic</u> NP 0.6 (10.7) UC -2.1 (7.0) Difference 2.7 p = 0.18	<u>Specialty Physician Office</u> NP 0.6 (9.0) UC -1.9 (5.9) Difference 2.5 p = 0.14 <u>Inpatient Days</u> NP 0.2 (2.6) UC -0.3(1.8) Difference 0.5 p = 0.32	Resource use measured from the electronic medical record, according to total numbers of outpatient visits with healthcare providers and inpatient days at the UW Medical Center and affiliated hospitals/clinics during 2 years. Study not powered to detect differences in resource utilization

Hill, 2003 [55] RS ^ Outpatient / Specialized Referral 80 Rheumatoid arthritis (RA) outpatients, 18 years or older, to rheumatology clinic on at least three previous occasions; study period of 12 months, at a traditional rheumatology outpatient clinic managed by junior hospital doctors (JHDs) within a large teaching hospital, England	*Intervention* = Rheumatology NP (RNP) care (n =39) *Control* = Junior Hospital Doctor (JHD) care (n= 41)	<u>Lab tests</u> NP 5% (11/234 consultations) JHD 10% (23/226 consultations) <u>X rays</u> NP 2% (4/234) JHD 3% (7/234) No p-values reported	<u>GP visits</u> NP 1% (3/234) JHD 5% (12/226) <u>Referrals</u> NP 32% (75/234) JHD 12% (26/226) No p-values reported	Limited quality measurement: study authors report that all consultations / referrals to physicians and other health professionals were noted, but no indication of process Per protocol, actual treatment analysis

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT) #Post Hoc Analysis

Table I-7 Resource Utilization / Cost Endpoint-Outcomes: Primary Health Care

Statistically significant differences in 2 RS studies and 1 IPT study

Consult Time and Return Visits in *Patients with 'Common Complaints'* Primary Health Care RS
Direct Costs per Consult (Resource Use, Length of Consult, Follow-up Consults, Salary Costs); Direct Costs per Consult at Study NP Clinics versus Reference (no NP) Clinics, in *Patients with 'Common Complaints'* Primary Health Care RS (post hoc analysis)
Total Healthcare Charges in *Low-Income Maternal / Infant Patients*, Primary Health Care RS
NSAID Costs in *Patients with Chronic Non-malignant, Non-inflammatory Musculoskeletal Pain*, Primary Health Care IPT

No statistically significant differences in 1 IPT study

Cost Effectiveness of Continence Service for *Patients with Incontinence Symptoms*, Primary Health Care IPT (original study and post hoc analysis)

Author, Year **RS^ / IPT^^** **Setting** **Study Population, Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)		**Quality of Endpoint Assessment / Comments**
Dierick-van Daele, 2009 [67] RS ^ Primary Health Care (PHC) 1,591 PHC patients from 15 general practices, 16 years and older, with common complaints regarding respiratory / throat, ear / nose, musculoskeletal / skin injuries, urinary / gynaecological and geriatric problems Two week intervention	*Intervention* = patient care from newly graduated NP (Master Degree of Advanced Nursing Practice) experience ranging 1 to 5 years; 12 NPs (n = 817) *Control* = patient care from GP with an average of 16 years' experience; 50 GPs	<u>Mean (SD) duration of consultation</u> NP 12.22 minutes (5.7) GP 9.20 minutes (4.8) p < 0.001 <u>Investigations</u> NP 2.4% (18/747) GP 2.9% (19/650) p = 0.55 <u>Referrals</u> NP 12 % (90/747) GP 14.2 % (92/650 p = 0.24	<u>Asked to return</u> NP 50.3% (340/676) GP 41.3% (250/604) p = 0.001 <u>Returned for same problem</u> NP 23.5% (121/515) GP 18.3% (89/487) p = 0.040 <u>Mean (SD) length of absence from paid job due to illness</u> NP 1.11 days (0.32) GP 1.11 days	The research assistant recorded the length of each consultation from patient arrival at consultation room to departure There is no conclusive properties-information provided for the three questionnaires used for patient-specific data collection, but only a justification of their validity according to the study authors' assurance on discussion with 2 GPs with research experience. Subsequent to

within a study duration of 6 months; patients who attended a general practice on a day when the NP was present were invited to participate in the trial, Netherlands	(n = 684) Study practices were also compared to external reference practices where 17 GPs worked in 5 general practices without NPs		(0.31)	discussion with the 2 GPs, the questionnaires were next tested on a group of 40 patients, resulting in two textual refinements as well as "asking the name of the practitioner instead of the type of practitioner (NP or GP) consulted" Baseline differences in study design included a booking time set at 15 minutes for NPs versus 10 minutes set for GPs
#Dierick-van Daele, 2010 [27] Cost Minimization Evaluation **Post Hoc Analysis** to Dierick-van Daele (2009) RS ^ Primary Health Care (PHC) 1,591 PHC patients from 15 general practices, 16 years and older, with common complaints regarding respiratory / throat, ear / nose, musculoskeletal / skin injuries, urinary / gynaecological and geriatric problems Two week intervention within a study duration of 6 months; patients who attended a general practice on a day when the NP was present were invited to participate in the trial, Netherlands	*Intervention* = patient care from newly graduated NP (Master Degree of Advanced Nursing Practice) experience ranging 1 to 5 years; 12 NPs (n = 817) *Control* = patient care from GP with an average of 16 years' experience; 50 GPs (n = 684) Study clinics were also compared to reference clinics;17 GPs practiced in 5 reference clinics without NPs	**CONSULTS** 1) Mean (SD) direct costs within healthcare *per consult* Direct healthcare costs include resource use, length of consultations, costs of follow-up consultations, and salary costs NP €31.94 (€36.29) GP €40.15 (€49.94) Difference - €8.21 95% CI €3.56 to €12.85 p = 0.001 2) Mean (SD) 'direct and productivity costs' *per consult* NP €144.40 (€53.18) GP €145.87 (€67.15) Difference € –1.48 95% CI – €4.94 to €7.90	**CLINICS** continued: 2) Mean (SD) 'direct and productivity costs' *per consult* Study clinics with NPs €145.08 (€60.07) Reference clinics without NPs €141.09 (€63.03) Difference € 4.00 95% CI - €8.61 to € 0.61 p = 0.09 "For pragmatic reasons, data for follow-up consultations, length of consultations, and number of days of absence were only gathered in study practices. It was assumed	Inclusion of societal perspective, with costs *outside* the healthcare sector deemed productivity costs (productivity costs = lost productivity while away from work due to illness on sick leave days; indirect costs related to paid work outside the healthcare sector) Without calculation of an equivalence margin, the intervention and control groups were assumed to be equivalent based on the erroneous assumption that no significant differences in outcome or process measures found between NP or GP consultations represented equivalence (Dierick-van Daele, 2010, p. e33) between the intervention and control groups within study practices [102]

Feb. 17, 2017 €1.00 Euro = $1.53 Canadian €0.72 Euro = $1.00 Canadian		p = 0.65 **CLINICS** 1) <u>Mean (SD) direct costs within healthcare</u> *<u>per consult</u>* Study clinics with NPs Cost per consult €35.76 (€43.35) Reference clinics without NPs Cost per consult €39.21 (€42.99) Difference – €3.45 95% CI €0.22 to €6.68 p = 0.04	that these data were the same for the external reference group." (Dierick-van Daele, 2010, p.e30). Care provided by NPs in primary health care (PHC) was measured at lower direct costs for consults and lower direct costs for PHC clinics that integrated NPs. Cost differences were mainly caused by differences in annual salary (prices indexed as of 2006) NP €41,160.00 GP €94, 475.92	Cost minimization evaluation is a controversial method for cost evaluation of equivalence trials, performed when the health effects of the alternatives are known or assumed to be equal. In this case, the decision simply revolves around the costs. Only the costs need to be analysed, and the least costly alternative is the most efficient. However, few interventions are actually equally effective.[91]
Jones, 2002 [66] IPT ^^ Primary Health Care (PHC) 222 PHC patients from 5 general practices with computerized prescribing systems. Patients were 18 years or older, with non-malignant, non-inflammatory musculoskeletal pain and oral non-steroidal anti-inflammatory drug (NSAID) prescriptions covering 6 or more weeks of the last 12 months; 6 month study, with all patients examined at their	*'Active Intervention'* = NP assessment patient-tailored educational package with request that patients withdraw their NSAIDs and use appropriate alternative drug and non-drug therapies (e.g. strategies on weight reduction, use of local heat and cold, back and neck care, footwear, massage, and relaxation techniques) + Usual GP Care (n =110)	1) <u>Median Change in NSAID Costs</u> at 6 months (interquartile range) <u>Intervention</u> - £ 2.61 (-£14.65, £3.45) <u>Control</u> £0.00 (-£5.92, £11.00) Difference - £2.61 p = 0.008 2) <u>Median change in all drug costs</u> at 6 months (interquartile range) <u>Intervention</u> £ 24.53 (-£ 6.94, £ 47.26)	3) <u>Mean healthcare service cost per patient</u> at 6 months (interquartile range) <u>Intervention NP educational package</u> (excluding costs for telephone calls) £40.70 (£34.67, £46.40) <u>Control</u> no comparative cost provided 4) <u>Mean patient travel cost</u> at 6 months (interquartile range)	Five general practices represented a mix of rural / urban and fundholding / non-fundholding practices Changes in health service use, drug and patient costs were self-reported Not inclusive of all (societal) costs, one of which was the patients' additional purchase of drugs and equipment on advice of NP Both control and intervention groups were treated by the same single NP Time spent by NP (£16/hr) providing

general practice or their homes, England GALS screen (Gait, Arms, Legs & Spine) assessment to detect locomotor abnormalities related to musculoskeletal pain *Feb.17, 2017* £ 1.00 Great Britain = $1.62 Canadian £ 0.62 Great Britain = $1.00 Canadian	*'Control Intervention'* = same single NP provided assessment and basic education regarding NSAID use, reinforced with leaflet + Usual GP Care (n =112)	Control £ 10.75 (-£ 18.98,£ 47.00) Difference £ 13.78 p = 0.25 Total drug costs increased more in the intervention group vs control	Intervention (time & expense traveling to the practice office, but excluding purchases of drugs and equipment on the NP's advice) £ 0.83 per patient (£0.00, £1.25) Control no comparative cost provided	education advice and checking patient compliance, had no known comparison to 'cost per patient for regular GP service'
Hannan, 2012 [69] RS ^ Primary Health Care (PHC) 139 healthy first-time mothers, 18 years or older, each of whom delivered a healthy, full-term single infant; low-income family Intervention occurred for first 2 months post-birth, delivered offsite via telephone. Study patients were recruited from hospital prior to discharge, U.S. Recognizing that healthcare (HC) charges do not equal actual costs (including societal costs), the study's intent was only to provide a comparison of healthcare charges between groups. *Feb. 17, 2017* $1.00 U.S = $1.31 Canadian $0.76 U.S. = $1.00 Canadian	*Intervention* = follow-up phone-calls by NP with 'back-up' pediatric physician available for consultation (n =70) NPs were Masters prepared pediatric NPs with a minimum of 10 years' experience, at a salary of $40.21/ hour, from the AHEC (Area Health Education Center) data base *Control* = routine hospital discharge and a pediatrician appointment in 2 months (n =69)	Infant vaccinations at 2 months NP 92.8% (65/70) Control 84.1% (58/69) p = 0.186 Urgent-care-centre visits at 2 months NP 3.6% (5/139) Control 2.2% (3/139) p = 0.48 Mean (SD) charges, Urgent-care-centre NP $376 ($27) range $294-$482 Control $351($15) range $267–$402 p = 0.47 Emergency room (ER) visits at 2 months NP 7.2% (10/139) Control 11.5% (16/139) p = 0.179 Mean (SD) HC charges, ER NP $104 ($267) range $365-$ 1,080 Control $245 ($538) range $298-$ 2,410 p = 0.13	Hospitalizations at 2 months NP 0.7% (1/139) Control 2.2% (3/139) p = 0.30 Mean (SD) HC charges hospitalizations NP $51 ($423) range $3,547 for 1 hospitalization Control $764 ($3,847) range $9,153–$24,012 p = 0.29 Total charges NP phone service $1,598 (SD = $7.61) Average total charges phone-calls per mother $23.83 Total healthcare charges per group at 2 months NP $14,333 Control $70,834 Difference $56, 501 p < 0.05	Healthcare utilization data derived from self-report and infants' medical records obtained from the care facility or the mothers; no designation of societal cost Attrition: 7/70 (10%) intervention mothers were unable to be contacted post-discharge due to dis-connected telephones NP follow-up telephone calls to low-income first time mothers with healthy full term infants was an easily applied intervention at a relatively low cost, for management of maternal and infant health outcomes as per study

Williams, 2005 [60] IPT ^^ Primary Health Care (PHC) 3746 PHC patients aged 40 years and over living in private households, with incontinence several times per month or more, or several times a year, and reported impact of symptoms on quality of life Six month intervention period, at patients' homes in Leicestershire and Rutland, England *Feb.17, 2017* £ 1.00 Great Britain = $1.62 Canadian £ 0.62 Great Britain = $1.00 Canadian	*Intervention* = continence service provided by NPs (n = 2958) *Control* = existing usual primary care including GP and continence advisory services (n =788) 4:1 ratio was deemed necessary to ensure sufficient intervention data for evaluation of detrusor muscle over-activity (wall of bladder) and urodynamic stress incontinence (involuntary leakage of urine with increased intra-abdominal pressure in the absence of detrusor contraction)	<u>Cost-effectiveness according to number of symptoms alleviated, at 6 months</u> In the 3rd - 6th months of study, costs generated by the NP service were similar to months 1-3, while the overall difference in mean number of symptoms alleviated remained the same, resulting in an incremental 'cost / additional symptom alleviated' that was greater at 6 months (£488) than at 3 months (£242) No p-values reported		<u>Incomplete reporting</u> 76% of the entire study population were not included in the cost-effectiveness analysis (CEA). Cost data represents only 24% (905/3746) of all study patients; of this 24%, 19% (171/905) patients were control patients, and 81% (734/905) were intervention patients <u>Inconclusive</u> 1) Inconsistent sourcing of data upon which CEA was based, integrating published cost data for control, and only using data estimates not similarly verifiable, for intervention cost 2) No tabled data regarding type of resource use (healthcare visits / medications / appliances) with no associated stratified cost data comprising the CEA numbers for the reader to critically appraise No designation of societal cost Higher start-up costs / longer consults limited cost-effectiveness of this study's intervention service (designed for this study) versus standard clinic practice
#Williams, 2011 [81] **Post Hoc Analysis** 6 year follow-up to Williams (2005)	*Intervention* = continence service provided by NPs	<u>Mean (SD) 'Total National Health Service Costs + Own Costs'</u> collected retrospectively over 6 months	<u>Female Intervention</u> £114.18 (£29.18) (95% CI £56.95 to £171.40)	At long term follow-up, cost data was available for 81% (2217/2728) cases, with multiple imputation used to address missing data.

IPT ^^ Primary Health Care (PHC) *Feb.17, 2017* £ 1.00 Great Britain = $1.62 Canadian £ 0.62 Great Britain = $1.00 Canadian The NP continence service was designed for the trial, and funded only for the duration of the research program. This NP service was not funded to operate throughout the interim period of 6 years Service expired at unknown time post original trial (that occurred 6 years prior) England	(n = 2958) *Control* = existing usual primary care including GP and continence advisory services (n =788) 4:1 ratio was deemed necessary to ensure sufficient intervention data for evaluation of detrusor muscle over-activity (wall of bladder) and urodynamic stress incontinence (involuntary leakage of urine with increased intra-abdominal pressure in the absence of detrusor contraction)	prior to follow-up study, with study authors noting they were unable to ask about the whole 5-7 year period due to unreliable recall (Williams, 2011, p. 3) <u>Male Intervention</u> £93.97 (£48.17) (95% CI £-0.55 to £188.49) <u>Male Control</u> £65.50 (£36.43) (95% CI £ -5.99 to £136.99) p = 0.3	<u>Female Control</u> £87.67 (£12.36) (95% CI £63.44 to £111.91) p = 0.2	Inconclusive, related to: 1) Inconsistent sourcing of data upon which CEA was based, integrating published cost data for control, and only using data estimates not similarly verifiable, for intervention cost. 2) No tabled data regarding type of resource use (healthcare visits / medications / appliances) and no stratified cost data unique to each group, as basis for computed CEA values. No designation of societal cost.

*Primary Endpoint ^Role Substitution (RS) ^^Interprofessional Team (IPT) #Post Hoc Analysis

Table I-8 Overall / Global Quality of Life Endpoint-Outcomes (SF-36 or derivations)

Statistically significant differences in 1 IPT^^ study

Physical and mental components of the SF-12 Questionnaire, *Post-operative Women with Suspected Ovarian Cancer*, Outpatient IPT

No statistically significant differences 2 RS studies and 6 IPT studies

Soft Tissue Injury Emergency Department Patients, Acute RS
Internal Medicine Inpatients, Acute RS
Cardiovascular Disease Patients, Outpatient IPT
Cardiac Surgery Patients, Outpatient IPT
Coronary Artery Bypass Graft (CABG) Surgery Patients, Outpatient IPT
COPD Patients, Outpatient IPT (pilot study)
Breast cancer survivors with abruptly recurred menopause, Outpatient IPT
Patients with Chronic Non-malignant, Non-inflammatory Musculoskeletal Pain, Primary Health Care IPT

Author, Year **RS^ / IPT^^** **Setting** **Study Population, Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)	**Quality of Endpoint Assessment / Comments**
McCorkle, 2009[52] IPT ^^ Outpatient / Specialized Referral 149 post-surgical outpatients 21 years or older, suspected primary diagnosis of ovarian cancer after abdominal surgery, prognosis of at least 6 months, with an order to initiate chemotherapy; patient contact made at private homes or by telephone, U.S.	*Intervention* = 18 contacts by an oncology NP, supported by psychiatric NP (PSYNP) consults (32/74 intervention patients) when warranted for high emotional distress = Distress Thermometer > or = to 4 (n=74) *Attention Control* = nine contacts by research assistant, supported by medical social worker (no data for patient contact with social worker) (n = 75)	QOL measured at baseline (24–48 hours after surgery) 1, 3, and 6 months post-surgery Adjusted QOL baseline scores were included as covariates in **3 types of mixed effect regression models,** built to estimate **'rates of change'** in different QOL measures over time: **(1) Oncology NP without PSYNP** Effect Estimates (EE) <u>SF-12 physical component</u> EE = - 0.07599 ± se 0.02425 p = 0.0019 The rate of improvement was significantly greater for control than intervention <u>SF-12 mental component</u> EE = 0.01776 ± se 0.01138 p = 0.1195 Non-significant rate of change in intervention vs control	Endpoint assessment based on reliable, valid, and standardized tool, the Short Form-12version2 (SF-12v2) Baseline measures were obtained prior to randomizatio n, with significant differences found in scores on the SF-12 mental component

	Overall / global quality of life endpoints: SF-12 tool, derived from the Medical Outcomes Short-Form 36 (SF-36) a) physical component b) mental health component Higher scores indicate better health	**(2) Oncology NP with PSYNP** Effect Estimates (EE) SF-12 physical component Poor model fit – no EE data SF-12 mental component EE = 0.02300 ± se 0.00748 p = 0.0023 The rate of improvement in the SF-12 score was significantly greater for intervention vs control **(3) PSYNP without Oncology NP** Effect Estimates (EE) SF-12 physical component EE = 0.1948 ± se 0.03877 p < 0.0001 SF-12 mental component EE = 0.06558 ± se 0.01676 p = 0.0001 The PSYNP component significantly increased the rate of improvement over time in both SF-12 measures	and lower baseline QOL in the intervention group. Baseline QOL scores were adjusted for model testing; final covariates included age, marital status, number of comorbiditie s, disease status (recurrence or not) and education level
McClellan, 2012 [63] RS ^ Acute Emergency Department 372 peripheral soft tissue injury patients older than 16 years eligible for management by any of 3 professionals: Emergency NP (ENP), Extended Scope Physiotherapist (ESP), Emergency Department (ED) Doctor. Eight week study period at a single inner city ED, England	*Intervention* = patient management from arrival to discharge by ENP or ESP ENP group (n = 123) ESP group (n =126) *Contro*l = routine ED doctor care (n = 123)	Overall Quality of Life at 8 weeks SF-12v2, Physical Component 95% CIs Dr −3.8-10.1 (3.2) 68/123 patients ESP 0.2-4.6 (2.4) 72/126 patients ENP 1.6-6.5 (4.1) 73/123 patients NPs and ESPs were reported to be clinically equivalent to routine care provided by doctors	Main analysis was by intention to treat. A per-protocol analysis was reported to have also been undertaken, though no per protocol data is shown.
Pioro, 2001 [71] RS ^ Acute Inpatient 381 heterogeneous internal medicine	*Intervention* = NP-based care (n=193) *Contro*l=House-staff care	Quality of Life SF-36 at 6 weeks following discharge Between group differences were not statistically significant p > 0.1	Endpoint assessed with the reliable and valid Medical Outcomes

inpatients, 18–69 years, from hospital admission to 6 weeks post-discharge at single center teaching hospital, U.S.	(n=188)		Study Short Form 36 (SF-36)
Tranmer, 2004 [46] IPT ^^ Outpatient / Specialized Referral 200 postoperative cardiac surgery outpatients discharged from first cardiac surgery with no stay at Intensive Care Unit (ICU) Five week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge, eastern Canada	*Intervention* = Usual Care + NP initiated phone contacts for patients in 1st 5 weeks following hospital discharge (n= 102) *Control* = Usual Care (UC) including education booklet, home-care follow-up as necessary, and NP contact information, with instruction to call with questions or concerns (n= 98)	*<u>Mean (SD) Quality of Life</u> 5 Weeks <u>Physical component</u> NP 36.3 (6.4) (92/102 patients) UC 36.2 (7.5) (92/98 patients) Mean difference 0.04 (95% CI –1.99 to 2.08) p = 0.97 <u>Mental component</u> NP 50.4 (11.5) (92/102 patients) UC 51.7 (11.9) (92/98 patients) Mean difference –1.25 (95% CI –4.54 to 2.04) p = 0.45	Endpoint assessed with reliable and valid Medical Outcomes Study Short Form 36 (SF-36)
Goessens, 2006 [47] IPT ^^ Outpatient / Specialized Referral <u>Cardiovascular disease</u> (CVD) Peripheral arterial disease Abdominal aortic aneurysm Cerebrovascular disease Coronary heart disease 236 CVD outpatients with two or more modifiable risk factors: smoking, hypertension, dyslipidemia, diabetes, obesity, hyperhomocysteinemia 1 year intervention at risk-factor management clinic, Netherlands	*Intervention* = NP at risk factor management clinic + Usual Care (n=119) *Control* = Usual Care (UC) by GP and treating vascular specialist (n=117)	<u>Overall quality of life at one year</u> No significant differences between group scores on the medical outcomes study short form-36 (SF-36) No individual data shown	Despite significant reduction in CVD risk factors for high-risk patients (see Appendix I-2) no significant differences in overall, global quality of life measures were found after one year of NP intervention, using the Medical Outcomes Study Short Form 36 (SF-36)

Sawatsky, 2013 [48] IPT ^^ Outpatient / Specialized Referral 204 postoperative cardiac surgery outpatients following first time coronary artery bypass graft (CABG) surgery Six week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge. Patients with significant issues / concerns were seen at an NP Follow-up (NPFU) Clinic, western Canada	*Intervention* = = Usual Care + NP phone contact at 2-3 days post discharge for needs assessment, with recommendations to follow-up with primary care provider, cardiac surgeon, receive additional phone contact from NP, go to NPFU clinic, or to local Emergency Department (n= 97) *Control* = Usual Care (UC) including advice to make primary care provider appointment within 1 week; return visit to cardiac surgeon was scheduled for all patients at 6 weeks (n=107)	* <u>Mean (SD) Quality of Life</u> Physical component 2 weeks NP 19.0 (3.4) UC 18.0 (3.4) p = 0.04 6 weeks NP 22.2 (4.2) UC 22.0 (4.0) p = 0.69 Mental component 2 weeks NP 21.5 (2.1) UC 21.5 (2.3) p = 0.87 6 weeks NP 21.3 (2.3) UC 21.1 (2.3) p = 0.67	Endpoint assessed with reliable and valid Medical Outcomes Study Short Form 36 (SF-36) Disruption of randomized sample: once intervention was established, several control patients were pulled from trial, deemed too ill for the study (Sawatsky, 2013, p. 2085)
Berkhof, 2014 [50] IPT ^^ Outpatient / Specialized Referral **Pilot study** 100 chronic obstructive pulmonary disease (COPD, a progressive disease) outpatients > or = to 40 years, COPD GOLD stage > or = to 2 (Global initiative for staging Obstructive Lung Disease: 1 = mild; 4 = very severe) smoking history >10 pack-years; 2 year study at a large teaching hospital, Netherlands	*Intervention* = patient-initiated outpatient visits with pulmonary NP upon increase of symptoms (dyspnea, cough, sputum, hemoptysis, or thoracic pain); NP followed an 'on-demand protocol' that included consult with pulmonologist for urgent problems (n = 49) *Control*= usual care (UC) of traditional outpatient visits initiated by pulmonologist, to the pulmonologist or the pulmonary NP (n=51)	<u>Overall quality of life</u> at two years No significant differences between groups, while 3/8 component scores on SF-36 met the minimal clinically important difference (MCID)	Less deterioration in disease-specific health status for intervention patients was not accompanied by significant differences in overall quality of life measures using the SF-36 tool

Ganz, 2000 [61] IPT ^^ Outpatient / Specialized Referral 76 breast cancer survivor outpatients with abruptly recurred menopause symptoms due to discontinued estrogen replacement therapy (ERT) related to breast cancer; intervention period of 4 months at an outpatient clinic, U.S.	*Intervention* = comprehensive menopausal assessment or CMA (targets highly symptomatic women with goal of reducing symptoms and improving quality of life, through education, counseling, and focused non-ERT interventions) delivered by NP (n=37) *Control* = usual care (UC) + 1 contact from research assistant at 2 months asking of therapies used for symptom management (n= 39)	<u>Vitality</u> at 4 months Vitality, a dimension of health-related quality of life on the SF-36 tool, showed no significant between-group differences p = 0 .77	Potential side effects to clonidine (fatigue, headache) used to treat 'hot flashes' in 39% of intervention patients, may have limited detection of intervention effect on SF-36 Vitality Scale
Jones, 2002 [66] IPT ^^ Primary Health Care (PHC) 222 patients 18 years or older, with non-malignant, non-inflammatory musculoskeletal pain and oral non-steroidal anti-inflammatory drug (NSAID) prescriptions covering 6 or more weeks of the last 12 months; 6 month study, all patients examined at their general practice or their homes, England <u>GALS screen</u> (Gait, Arms, Legs & Spine) assessment to detect locomotor abnormalities related to musculoskeletal pain	*'Active Intervention'* = NP assessment, patient-tailored educational package with request that patients withdraw their NSAIDs and use appropriate alternative drug and non-drug therapies (e.g. strategies on weight reduction, use of local heat and cold, back and neck care, footwear, massage, and relaxation techniques) + Usual GP Care (n =110) *'Control Intervention'* = (same single NP provided assessment and basic education regarding NSAID use, reinforced with leaflet) + Usual GP Care (n =112)	<u>Quality of Life</u> at 6 months on SF-36 No significant differences between groups	NSAID reduction: number of patients taking NSAIDs and dose of NSAID taken, may not be associated with deterioration in patients' overall health status

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT) #Post Hoc Analysis

Table I-9 Patient Satisfaction Endpoint-Outcomes

Statistically significant differences in 4 RS studies & 3 IPT studies

Communication *Minor Injury Emergency Department Patients*, Acute RS
Parents of Infants / Children with Atopic Dermatitis (Eczema), Outpatient RS
Rheumatoid Arthritis Patients, Outpatient RS
Patients with 'Common Complaints' and at least One Chronic Disease, Primary Health Care RS
Quality of Service and 'Amount of Help Received' for *Coronary Artery Bypass Graft (CABG) Patients*, Outpatient IPT
Achieving Best Recovery Possible and Side Effect Information for *Cardiac Surgery Patients*, Outpatient IPT
Perception of Problem in *Patients with Incontinence Symptoms*, Primary Health Care IPT (original study and post hoc analysis)

No statistically significant differences in 1 IPT study

Older Adults Discharged Home three months post-discharge, Outpatient IPT (pilot study)

Author, Year **RS^ / IPT^^** **Setting** **Study Population, Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)	**Quality of Endpoint Assessment / Comments**
Cooper, 2002 [62] RS ^ Acute Emergency Department 204 patients over 16 years, with minor injury that fell within the ENP (emergency NP) protocol, at a single Accident and Emergency (A & E) Department; 2 month study duration, Scotland	*Intervention* = ENP-led care (n = 102) *Control* = Senior House Officer (SHO)-led care (n = 102)	Patient Satisfaction Questionnaires regarding <u>patient-provider communication</u> were returned immediately after treatment Patients reported it was easier to talk to ENPs NP 97.6 (85/102) SHO 84.0 (81/102) p = 0.009 Patients given information on accident and illness prevention NP 75.3 (81/102) SHO 45.2 (73/102) p = 0.001 Patients given enough information on their injury NP 95.2 (83/102) SHO 82.5 (80/102) p = 0.007	Endpoint assessment based on a questionnaire modified from a previously validated questionnaire by Jenkins & Thomas (1996) However, limitations inherent to all self-completion questionnaires include: 1) refusal to complete / return the questionnaire leads to bias if non-responders

		Overall patient satisfaction NP 98.8 (85/102) SHO 87.7 (81/102) p < 0.001 Patient felt able to ask questions NP 94.0 (84/102) SHO 83.8 (80/102) p = 0.123 Patient understood advice received NP 94.1 (85/102) SHO 84.6 (78/102) p = 0.080 Patient felt that the providers listened NP 97.7 (87/102) SHO 86.4 (81/102) p = 0.089 Patient was given enough provider time NP 95.3 (86/102) SHO 82.5 (80/102) p = 0.12	differ from responders 2) Patients may ask other people to assist in completing the questionnaire, or even complete it on their behalf, prejudicing the sample 3)Lack of ability to read (low literacy levels / illiteracy in patients) may contribute to nonresponse
Sawatsky, 2013 [48] IPT ^^ Outpatient / Specialized Referral 204 postoperative cardiac surgery outpatients following first time coronary artery bypass graft (CABG) surgery Six week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge. Patients with significant issues/concerns were seen at an NP Follow-Up (NPFU) Clinic, western Canada	*Intervention* = Usual Care + NP phone contact at 2-3 days post discharge for needs assessment, with recommendations to follow-up with primary care provider, cardiac surgeon, receive additional phone contact from NP, go to NPFU clinic or to local ED (n= 97) *Control* = Usual Care, including advice to make primary care provider appointment within 1week; return visit to cardiac surgeon was scheduled for all patients at 6 weeks (n=107)	<u>Patient satisfaction</u> Intervention patients were significantly more satisfied with post-discharge care compared to usual care patients 1) <u>Quality of Service</u> at 2 and 6 weeks respectively p = 0.003 and 0.005 2) <u>Amount of Help Received</u> at 2 and 6 weeks respectively p = 0.001 and 0.002 No individual data shown	Endpoint assessment based on two questions from the reliable and valid 'Client Satisfaction Questionnaire' (CSQ-8)

Tranmer, 2004 [46] IPT ^^ Outpatient / Specialized Referral 200 postoperative cardiac surgery outpatients discharged from first cardiac surgery with no stay at Intensive Care Unit (ICU) Five week study intervention delivered offsite via telephone; study patients recruited from hospital prior to discharge, eastern Canada	*Intervention* = Usual Care + NP initiated phone contacts for patients in 1st 5 weeks following hospital discharge (n= 102) *Control* = Usual Care (UC) including education booklet, home-care follow-up as necessary, and NP contact information, with instruction to call with questions or concerns (n= 98)	<u>Patient satisfaction at 5 weeks</u> (scores from 5-point measurement scale were standardized to scores out of 100) 'Achieving best recovery possible' NP 71.3 UC 63.5 p = 0.03 Side effect information NP 61.5 UC 54.0 p = 0.05 Help with decisions about care NP 66.6 UC 59.0 p = 0.06 Knowing what to expect during recovery NP 70.3 UC 65.7 p = 0.23 Complication information NP 63.2 UC 56.7 p = 0.11 Recognizing potential problems NP 59.6 UC 56.7 p = 0.48 Identifying depressive feelings NP 51.0 UC 46.9 p = 0.32 <u>Overall mean (SD) 'satisfaction with recovery'</u> NP 60.5 (20.4) UC 55.7 (20.8) p = 0.08	Cronbach's alphas 0.96 and 0.95 for satisfaction scale and heart-specific scale according to study conducted by Shortell et al. (2000) re post-operative outcomes in 3,045 cardiac procedure patients
Schuttelaar, 2010 [59] RS ^ Outpatient / Specialized Referral 160 patients < 16 years, 80 patients aged < or = to 4 years and 80 patients aged 4–16 years, all new referrals from GPs or pediatricians with a diagnosis of atopic dermatitis (eczema); one year study at an outpatient clinic, Netherlands	*Intervention* = NP-led care (n = 81) Age < or = to 4 years (n = 40) Age 4-16 years (n = 41) *Control* = conventional care by dermatologist (n = 79) Age < or = to 4 years (n = 40) Age 4-16 years (n = 39)	<u>Mean (SD) Patient satisfaction</u> 4 months NP 27.1 (3.9) Control 24.4 (3.4) p < 0.001 8 months NP 27.3 (4.0) Control 24.3 (3.3) p < 0.001 12 months NP 26.9 (4.9) Control 24.8 (4.3) p < 0.023	Endpoint assessment used the reliable and valid 'Client Satisfaction Questionnaire-8' (CSQ-8), <u>completed by parents</u> at 4, 8, and 12 months

Hill, 2003 [55] RS ^ Outpatient / Specialized Referral 80 Rheumatoid arthritis (RA) outpatients, 18 years or older, to clinic on at least 3previous occasions; study period of 12 months, at traditional rheumatology clinic managed by junior hospital doctors (JHDs) within a large teaching hospital, England	*Intervention* = Rheumatology NP (RNP) care (n =39) *Control* = Junior Hospital Doctor (JHD) care (n= 41)	<u>Median (range) Patient satisfaction</u> at 48 weeks NP total scores increased from baseline 3.57 (2.3 – 4.9) to 4.1 (2.4 – 4.9) JHD total scores decreased from baseline 3.60 (2.1 – 4.8) to 3.56 (2.4 – 4.7) $p < 0.001$ A number of JHDs were involved in the study versus only one RNP, resulting in bias associated with the NP intervention (with one NP, cannot calculate variability through SD, for integration into effect estimate calculations)	Endpoint assessment used the reliable and valid Leeds Satisfaction Questionnaire (Hill et al., 1992) A rheumatology NP may bring benefit of enhanced patient satisfaction , related to potentially greater symptom control, as per study
Enguidanos, 2012 [65] IPT ^^ Outpatient / Specialized Referral **Pilot study** 199 at-risk older adults discharged home from hospital without in-home care (e.g. home health or hospice) or able / available caregivers; 6 month study set in a managed care medical center, or Health Maintenance Organization (HMO), patients recruited from hospital prior to discharge, U.S.	*Intervention* = Brief NP Transition, a 'bridge' of up to 3 home visits, 2 phone calls from primary health care NP, within 72 hours of discharge (n = 100) *Control* = standard medical care, including access to case management services (wait time 2-14 days) (n =99)	<u>Patient satisfaction</u> at 3 months No significant differences between groups	Endpoint assessment used the reliable and valid Home Care Satisfaction Measure: 'test-retest reliability' 0.68-0.88 and high concurrent validity 0.26-0.76 Small sample size (pilot study) and attrition on follow-up surveys (~ a 65% response rate) limited detection of between-groups differences
Dierick-van Daele, 2009 [67] RS ^ Primary Health Care (PHC)	*Intervention* = patient care from newly graduated NP (Master Degree of Advanced Nursing Practice) experience ranging from 1 to 5 years; 12 NPs	<u>Mean (SD) Patient perceptions of quality of care</u> at 6 months NP 8.19 (1.18) GP 8.20 (1.26) $p = 0.83$	No conclusive properties-information provided for the questionnaires, but only a justification of questionnaires' validity according to

1,591 PHC patients from 15 general practices, 16 years and older, with common complaints regarding respiratory / throat, ear / nose, musculoskeletal / skin injuries, urinary / gynaecological and geriatric problems Two week intervention within a study duration of 6 months; patients who attended a general practice on a day when the NP was present were invited to participate in the trial, Netherlands	(n = 817) *Control* = patient care from GP with an average of 16 years' experience; 50 GPs (n = 684) Study practices were also compared to external reference practices where 17 GPs worked in 5 general practices without the involvement of NPs	Statistically significant improvement in patient satisfaction was only found for <u>patients in NP group who reported at least one chronic disease</u> (583/1591 patients) NP 8.35(1.07) UC 8.11 (1.32) p = 0.02	study authors' assurance on discussion with 2 GPs with research experience. Questionnaires were next tested on 40 patients, resulting in two textual refinements as well as asking the name of the practitioner instead of the type of practitioner (NP or GP) consulted (Dierick-van Daele, 2009, p. 394)
Williams, 2005 [60] IPT ^^ Primary Health Care (PHC) 3746 PHC patients aged 40 years and over living in private households, with incontinence several times per month or more, or several times a year, and reported impact of symptoms on quality of life. Six month intervention period, at patients' homes in Leicestershire and Rutland, England	*Intervention* = continence service provided by NPs (n = 2958) *Control* = existing usual primary care including GP and continence advisory services (n =788) 4:1 ratio was deemed necessary to ensure sufficient intervention data for evaluation of detrusor muscle over-activity (wall of bladder) and urodynamic stress incontinence	<u>Patient Satisfaction</u> <u>3 months</u> NP 52% (1294/2498) Control 45% (276/618) Difference 7% (95% CI 3 to 12) p = 0.001 <u>6 months</u> NP 64% (1428/2236) Control 53% (289/546) Difference 11% (95% CI 6 to 16) p < 0.001 <u>Patient Perception of Problem as Mild or None</u> <u>3 months</u> NP 74% (819/2468) Control 68% (416/614) Difference 6% (95% CI 2 to 10) p = 0.003 <u>6 months</u> NP 79% (1721/2181) Control 70% (380/545) Difference 9% (95% CI 5 to 13) p < 0.001	Satisfaction with services was reported descriptively by patients' answer to an open-ended exploratory question, with no reference made to the method used for conversion of qualitative answers to quantitative results

#Williams, 2011 [81] **Post Hoc Analysis** 6 year follow-up to Williams (2005) IPT ^^ Primary Health Care (PHC) The NP continence service was designed for the trial, and funded only for the duration of the research program. This NP continence service was not funded to operate throughout the interim period of 6 years. Service expired at unknown time post original trial, 6 years prior, England	*Intervention* = continence service provided by NPs (n = 2958) *Control* = existing usual primary care including GP and continence advisory services (n =788) 4:1 ratio was deemed necessary to ensure sufficient intervention data for evaluation of detrusor muscle over-activity (wall of bladder) and urodynamic stress incontinence	<u>Patient Satisfaction; Patient Perception of Problem as Mild or None</u> at 6 year follow-up Between groups differences diminished after 6 years, becoming non-significant, with results in the direction of the NP continence service: <u>Patient Satisfaction</u> NP 55% Control 52% Difference 3% 95% CI -2 to 7% p = 0.2 <u>Patient Perception of Problem as Mild or None</u> NP 70% Control 69% Difference 1% 95% CI -3 to 5% p = 0.6	Inconclusive: Measurement of the long term effect of an expired program with no specification as to the expiry date of the program leaves no accuracy for interpretation of its long term effect. Continence services available post-trial for each group were identical, including the education and experience of NPs trained within the trial program, but without the continence program per se actively in place

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT) #Post Hoc Analysis

Table I-10 Other Endpoint-Outcomes

Statistically significant differences in 2 RS studies and 2 IPT studies

Perceived Maternal Health, Perceived Maternal Stress in *Low-Income Mothers*, Primary Health Care RS
Quality of Clinical Documentation in *Minor Injury Emergency Department Patients,* Acute RS
Knowledge and Perceived Risk of Sexually Transmitted Infection in *Female College Students (child-bearing age)*, Primary Health Care IPT
Self-Efficacy in *Type 1 Diabetes Patients,* Outpatient IPT (pilot study)

No statistically significant differences in 2 RS studies and 2 IPT studies

Patient Knowledge in *Rheumatoid Arthritis Patients*, Outpatient RS
Family Impact in *Families of Infants / Children with Atopic Dermatitis (Eczema),* Outpatient RS
Self-Care Efficacy in *Older Adults Discharged Home*, Outpatient IPT (pilot study)
Self-Efficacy in Management of Cardiovascular Risk Factors, *Cardiovascular Disease Patients*, Outpatient IPT (post hoc analysis)

Author, Year **RS^ / IPT^^** **Setting** **Study Population, Duration, Site**	**Intervention**	**Results** (Outcome data analyzed by Intention to Treat, ITT, on the basis of all randomized patients, as randomized, unless otherwise noted)	**Quality of Endpoint Assessment / Comments**
Hannan, 2012 [69] RS ^ Primary Health Care (PHC) 139 healthy first-time mothers, 18 years or older, each of whom delivered a healthy, full-term single infant; low-income family Intervention occurred for first 2 months post-birth, delivered offsite via telephone. Study patients were recruited from hospital prior to discharge, U.S.	*Intervention* = follow-up phone-calls by pediatric NP with 'back-up' pediatric physician available for consultation (n =70) *Control* = routine hospital discharge and a pediatrician appointment at 2 months (n =69)	<u>Maternal / Infant Health</u> at 2 months <u>Mean (SD) Perceived Maternal Health</u> NP 18.61 (1.74) Control 17.2 (2.69) $p < 0.0004$ <u>Mean (SD) Perceived Maternal Stress</u> NP 14.71(3.95) Control 24.64(4.61) $p < 0.0001$	Good internal and test-retest reliability; good validity for Perceived Stress Scale (PSS), Multidimensional Scale of Perceived Social Support (MSPSS) and for the Maternal Perception of Health Rating Scale (MPHRS). Research assistant collected data related to

		Perception of Social Support Non-significant difference Infant Weight Gain Non-significant difference	infant health from infants' medical records or from mothers at two months post-discharge. Attrition: 7/70 intervention mothers unable to be contacted due to disconnected telephones
Johnson-Mallard, 2007 [70] IPT ^^ Primary Health Care (PHC) 104 female college students not yet exposed to any formal lectures regarding sexually transmitted infections (STIs); 18 - 48 years (child-bearing age) presumably in good health at baseline; study duration of two weeks, set at two different universities, U.S.	*Intervention* = a brief 30 minute educational / behavioral intervention delivered by an NP at one week (n =51) *Control* = no educational / behavioral intervention (n = 53) A one-time educational / behavioural intervention was delivered to the experimental group one week after the pretest was given to both groups; post-test for both groups two weeks after pretest	Mean (SD) STI knowledge survey (higher scores indicate greater knowledge) at 2 weeks NP 26.1 (2.6) Control 21.0 (2.3) $p < 0.0001$ Mean (SD) perceived risk of STI survey (lower scores indicate lower perceived risk) at 2 weeks NP 4.0 (1.0) Control 7.9 (2.3) $p < 0.0001$	'STI Knowledge Survey' (STIKS, 1998): content validity at 0.93 and reliability at 0.76 Findings may assist NPs in reducing knowledge gaps related to STI morbidity associated with reproductive health: pelvic inflammatory disease, chronic pelvic pain, infertility, ectopic pregnancy, compromised birth outcomes (premature delivery, stillbirths, neonatal deaths, and infant disorders), and cervical cancer

Hill, 2003 [55] RS ^ Outpatient / Specialized Referral 80 Rheumatoid arthritis outpatients, 18 years or older, to rheumatology clinic on at least three previous occasions; study period of 12 months, at a traditional rheumatology outpatient clinic managed by junior hospital doctors (JHDs), within a large teaching hospital, England	*Intervention* = rheumatology NP (RNP) care (n =39) *Control* = junior hospital doctor (JHD) care (n= 41)	<u>Median (range) Patient Knowledge</u> at 48 weeks NP total scores increased from baseline 17 (9-28) to 21 (11–30) JHD total scores increased from baseline 21 (8–29) to 22 (12–30) No significant differences	Endpoint assessment based on the reliable and valid 'Patient Knowledge Questionnaire' a multiple-choice tool designed for use with rheumatoid arthritis patients (Hill et al., 1991)
Cooper, 2002 [62] RS ^ Acute Emergency Department 204 patients over 16 years, with minor injury that fell within the ENP (emergency NP) protocol, at a single Accident and Emergency (A & E) Department; 2 month study duration, Scotland	*Intervention* = ENP-led care (n = 102) *Control* = Senior House Officer (SHO)-led care (n = 102)	<u>Quality of Clinical Documentation,</u> scored out of 30, audited 4 months after the trial ended ENP 28.0/30.0 (94/102) SHO 26.6/30.0 (92/102) $p < 0.001$	'Documentation Audit Tool,' reliable and previously validated using an expert panel and a consensus methodology, scored out of 30 points (Cooper et al., 2000, double blind peer reviewed)
McCarrier, 2009 [7] IPT ^^ Outpatient / Specialized Referral **Pilot study** 78 Type 1 Diabetes Mellitus outpatients randomized, 21 -49 years with at least one A1c test > or = to 7% in previous 12 months; one year intervention period at the Diabetes Care Center (DCC multidisciplinary practice team includes physicians, NPs, on-site pharmacists, nurse educators, nutritionists, and mental health professionals) affiliated with the University of Washington Medical Center, U.S.	*Intervention* = NP coordination of Web-based care + usual care (n =42) *Control* = usual care (UC) from team at Diabetes Care Center (DCC) (n = 36)	<u>Diabetes-Specific Self-Efficacy</u> at 1 year NP + 0.14 (0.62) UC - 0.16 (0.62) Effect size = 0.30 (95% CI 0.01 to 0.59) p= 0.044	'Diabetes Empowerment Scale,' a measure of psychosocial self-efficacy, reliable and valid (Anderson et al., 2000)

Enguidanos, 2012 [65] IPT ^^ Outpatient / Specialized Referral **Pilot study** 199 at-risk older adults discharged home from hospital without in-home care (e.g. home health or hospice) or able /available caregivers; 6 month study set in a managed care medical center, or Health Maintenance Organization (HMO), patients recruited from hospital prior to discharge, U.S.	*Intervention* = Brief NP Transition, a 'bridge' of up to 3 home visits, 2 phone calls from primary health care NP, within 72 hours of discharge (n = 100) *Control* = standard medical care, including access to case management services (wait time 2-14 days) (n =99)	Efficacy in Self-Care at 6 months No significant differences between groups	'Efficacy in Self-Care Survey' with test-retest reliability at 0.82 - 0.89 and internal consistency at 0.77- 0.92 Attrition on follow-up self-efficacy surveys (66%; 131/199 outpatients) limited detection of between groups differences
#Sol, 2008 [75] **Post Hoc Analysis** to Goessens (2006) IPT ^^ Outpatient / Specialized Referral Cardiovascular disease (CVD) Peripheral arterial disease Abdominal aortic aneurysm Cerebrovascular disease Coronary heart disease 236 CVD outpatients with two or more modifiable risk factors: smoking, hypertension, dyslipidemia, diabetes, obesity, hyper-homocysteinemia One year intervention at a risk-factor management clinic in the University Medical Center Utrecht, Netherlands CVD is globally the most common cause of morbidity and mortality, influenced by multiple risk factors. New strategies are needed to reduce vascular risk; this post hoc study investigated whether changes in self-efficacy were related to changes in vascular risk factors	*Intervention* = NP at risk factor management clinic + Usual Care (n=119) Self-efficacy, a person's confidence to carry out the behaviour necessary to reach a desired goal, is theoretically, an important pre-condition for successful self-management and behavioural change. Goals for lifestyle change were monitored in context of self-efficacy promotion: encouraging feedback on self-management and performance attainment *Control* = Usual Care by GP and treating vascular specialist (n=117)	Self-Efficacy in Management of CVD risk factors No significant differences Self-efficacy was not associated with achievement of treatment goals	Limited quality measurement tool, adapted from a self-efficacy scale designed for Type II Diabetes Mellitus patients, not used before with CVD patients Study population was diverse and intervention focused on a variety of universal self-management tasks; wide scope may clarify non-significant differences in self-efficacy

Schuttelaar, 2010 [59] RS ^ Outpatient / Specialized Referral 160 patients < 16 years, 80 patients aged < or = to 4 years and 80 patients aged 4–16 years, all new referrals from GPs or pediatricians with a diagnosis of atopic dermatitis (eczema); one year study at an outpatient clinic, Netherlands	*Intervention* = NP-led care (n = 81) Age < or = to 4 years (n = 40) Age 4-16 years (n = 41) *Control* = conventional care by dermatologist (n = 79) Age < or = to 4 years (n = 40) Age 4-16 years (n = 39)	Family Impact Between groups differences were not statistically significant at baseline, 4, 8, or 12 months, nor for the separate age groups of children.	'Dermatitis Family Impact' questionnaire reliable and valid The impact of pediatric eczema on family may be similarly managed by NP as by dermatologist in a population representative of normal referrals from GP to specialist care

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT) #Post Hoc Analysis

Appendix J Results of NP Interventions on All Quantitative Patient Endpoint-Outcomes in Each of 29 RCTs

Author, Year Country Purpose **Level of Prevention**	**Design, Duration Setting**	**Patients (N)**	**NP Intervention Domains**	**Endpoints**	**Outcomes** Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	**Comments**
Pioro, 2001[71] U.S. To compare care delivered by NPs and house-staff, for general medical inpatients from admission to discharge **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment[13] *Feb. 17, 2017* $1.00 U.S = $1.31 Canadian $0.76 U.S. = $1.00 Canadian	RS^ Hospital admission to 6 weeks post-discharge; RCT conducted for 1.5 years *Acute Care Inpatient* Internal medicine wards at single center teaching hospital, Cleveland, Ohio, affiliated with Case Western Reserve University	381 unselected inpatients, 18–69 years, admitted for gastrointestinal, pulmonary, infectious, metabolic/ substance abuse, neurological, cardiovascular and "other" acute illnesses *Intervention* = NP-based care (n=193) *Contro*l=House-staff care (n=188)	Diagnosis Prescribing Clinical Procedures Education	1) *Adverse Events 2**)** *Resource & Cost 3)**Functional Status 4) **Global Quality of Life	1) *Overall Adverse Events (transfers to ICUs, hospital-acquired complications, and in-hospital mortality) NP 7.5% House-staff 11.8% Difference - 4.3% (95% CI -10.2, 1.6) p > 0.10 2) *Resource & Cost a. Mean length of hospital stay NP 5.0 days House-staff 5.3 days Difference -0.3 (95% CI -1.2, 0.6 days) p > 0.10 b. Mean number of consultations to other services (e.g. respiratory therapy) NP 1.4 House-staff 1.4 Difference -0.0 (95% CI -0.2, 0.3) p > 0.10 c. Mean total hospital charges, costs (U.S.$) NP $8854 House-staff $9426 Difference -$572 (95% CI -$2704, $1560) p > 0.10 d. Mean total ancillary charges, costs (U.S.$) NP $4960 House-staff $5358 Difference -$399 (95% CI -$1820, $1023) p > 0.10	Post-randomization breach (crossover of 89 NP patients to house-staff ward) in assignment of patients to groups, leading to possible selection bias (see Appendix G) It is unclear as to whether patient assignment post-randomization, truly represents selection bias: a systematic error that over or underestimates the intervention effect. An Unclear judgement may not be penalized with a No judgement[15] Incomplete reporting of raw data in Table 2: no fraction of patients comprising

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
					3) **Mean Change Functional Status a. Activities of daily living (ADL) NP 0.1 (76/193); House-staff 0.2 (86/188) Difference -0.1 (95% CI -0.5, 0.3) $p < 0.10$ b. Independent activities of daily living (IADL) NP 1.4 (76/193); House-staff 2.1 (86/188) Difference -0.7 (95% CI -1.4, 0.1) $0.05 < p < 0.10$ 4)**Global Quality of Life, SF-36 scores Differences not statistically significant $p > 0.1$	percentages reported No societal costs were reported, nor differences in salaries, costs of the medical director, or costs of off-hour coverage by residents
Allen, 2002 [44] U. S. To test the effectiveness of a nurse case management program to lower blood lipids in patients with coronary heart disease (CHD)	IPT ^^ Intervention for one year post-discharge *Outpatient / Specialized Referral* Outpatient clinic of Johns Hopkins Hospital, a large tertiary hospital, Baltimore, Maryland	228 coronary heart disease outpatients who received coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention, with hypercholesterolemia (low density lipoprotein cholesterol level >2.59 mmol/L	Diagnosis Prescribing Strategies for Behaviour Change Care coordination	1) *Lipid Goals: Total cholesterol Low density lipoprotein cholesterol (LDL-C, "bad" cholesterol) Triglyceride levels High density lipoprotein cholesterol	1) *Mean (SD) Lipid Levels at 1 year a. Total Cholesterol NP 4.1mmol/L (0.7) EUC 4.6mmol/L (0.6) Difference = 0.5 mmol/L, $p < 0.0001$ b. Low-density lipoprotein cholesterol (LDL-C) NP 2.2mmol/L (0.57) EUC 2.67mmol/L (0.57) Difference = 0.47 mmol/L, $p < 0.0001$ c. Triglycerides NP 3.57 mmol/L (1.53) EUC 4.25 mmol/L (1.79) Difference = 0.68 mmol/L, $p = 0.002$ d. High-density lipoprotein cholesterol (HDL-C) increased modestly in both groups	Attrition 31% with 69% (158/228) outpatients completing 12 month follow-up (77% NP patients; 62% UC patients) Incomplete reporting of raw data in Table II: no fraction of patients comprising percentages of dietary intake was reported

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
Tertiary Prevention reducing risks / threats to health in long-term chronic illness / permanent impairment [13] **Post hoc analysis, Paez (2006)** *Cost-effectiveness of nurse practitioner management of hypercholesterolemia following coronary revascularization* **Appendix I-6** *Feb. 17, 2017* $1.00 U.S = $1.31 Canadian $0.76 U.S. = $1.00 Canadian		or total cholesterol level > 5.18 mmol/L) *Intervention*= NP case management (individualized lifestyle and pharmacologic intervention) + Enhanced Usual Care (EUC) (n = 115) *Control* = Enhanced Usual Care (EUC) from primary providers &/or cardiologists including full lipid profiles at 4 weeks, 6 and 12 months after discharge, and goals for lipoprotein levels, diet and physical activity (n =113)		(HDL-C, "good" cholesterol) 2) **Drug Compliance 3) **Diet and Exercise	e. Achieved LDL-C goal < 2.59 mmol/L NP 65% EUC 35% Difference = 30% p = 0.0001 Hypercholesterolemia defined as LDL cholesterol level > 2.59 mmol/L or total cholesterol level > 5.18 mmol/L 2)**Medication compliance to lipid-lowering drugs at one year: NP 87% (100/115); EUC 79% (89/113) Difference 8% p = 0.10 3) **Diet and Exercise at 1 year Mean dietary intake (SD) in calories a. Total Fat NP 33.2% (+ or - 6.7%); EUC 34.6% (+ or - 6.5%) Difference 1.4% p = 0.009 b. Saturated Fat NP 10.1% (+ or - 2.2%); EUC 11.0% (+ or - 2.3%) Difference 1.1% p = 0.004 c. Dietary Cholesterol NP 254.2mg (+ or - 99.8 mg); EUC 292.0mg (+ or - 104.9 mg) Difference 37.8 mg p = 0.006 d. Dietary fiber NP 22.2 (+ or - 7.2); EUC 21.3 (+ or - 5.7) Difference 0.9 p = 0.28	Among patients on pharmacotherapy, 97% in both groups were taking a single statin agent: 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor Control of hypercholesterolemia in patients who have undergone coronary revascularization can be improved by NP case management as per study

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
					e. Exercise at 6 MET (metabolic equivalent) hours per week or more: NP 40% (46/115); EUC 26% (29/113) Difference 14% p = 0.02	
Jones, 2002[66] England To find out whether an NP-delivered educational package can reduce chronic oral non-steroidal anti-inflammatory drug (NSAID) usage in general practice <u>GALS screen</u> (Gait, Arms, Legs & Spine) assessment to detect locomotor abnormalities related to musculoskeletal pain	IPT^^ Six month study duration *Primary Health Care* Five general practices with computerized prescribing systems All patients examined at their general practice or their homes in Nottinghamshire	222 patients 18 years or older, with non-malignant, non-inflammatory musculoskeletal pain and oral non-steroidal anti-inflammatory drug (NSAID) prescriptions covering 6 or more weeks of the last year *'Active Intervention'* = NP assessment, patient-tailored educational package with request that patients withdraw their NSAIDs and use appropriate	Diagnosis Prescribing Education	1) *Self-reported reduction in oral NSAID dose at six months 2) **Changes in total prescription data, partially self-reported, alongside computer records of prescribing data 3) **NSAID costs; health service costs 4)**Global Quality of Life	1) *Self-reported reduction in oral NSAID dose by 50% or less, at 6 months Active NP Intervention 38 % (42/110) patients Control 13% (14/112) patients Difference = 25%, p < 0.0001 2) **Total prescriptions (median values and interquartile range) reported in terms of 'change in costs' at 6 months Active NP Intervention £ 24.53 (-6.94, 47.26) Control £ 10.75 (-18.98, 47.00) Difference= £ 13.78 p = 0.25 3)**Median change in NSAID cost at 6 months (interquartile range) Intervention -£ 2.61(-£14.65, £3.45) Control £0.00 (-£5.92, £11.00) Difference -£2.61, p = 0.008	Oral NSAIDS are one of the most widely used classes of drugs in the United Kingdom, particularly in older adults with osteoarthritis; significant inappropriate prescription or over-prescription of NSAIDs may contribute to morbidity (ulcer bleeding / ulcer perforation, NSAID toxicity), mortality and costs to health services and the patient Limitations: same single NP for both intervention and control groups, resulting in potential

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
Tertiary Prevention reducing risks / threats to health in long-term chronic illness / permanent impairment [13] *Feb.17, 2017* £ 1.00 Great Britain = $1.62 Canadian £ 0.62 Great Britain = $1.00 Canadian	Five general practices represented a mix of rural/urban and fundholding/non-fundholding practices	alternative drug and non-drug therapies (e.g. strategies for weight loss, use of local heat and cold, relaxation techniques) + Usual GP Care (n =110) *'Control Intervention'* = NP assessment and basic education regarding NSAIDs + Usual GP Care (n =112)			Mean (interquartile range) healthcare service costs per patient at 6 months Intervention Education Service (excluding phone calls) £40.70 (£34.67, £46.40) Control no comparative cost provided Patient travel costs (including time and expense traveling to the practice office; excluding purchases of drugs and equipment on the NP's advice) Intervention £ 0.83 (£0.00, £1.25) Control no comparative cost provided 4)**Overall quality of life at 6 months on SF-36 No significant differences between groups	bias; 'social desirability' where active intervention provided advice for reduction of NSAID use Not inclusive of all (societal) costs, one of which was the patients' additional purchase of drugs and equipment on advice of NP
Ansari, 2003 [45] U.S. **Pilot RCT**	IPT ^^ Two levels of individual randomization 74 providers (internal medicine doctors,	169 CHF outpatients individually randomized into three groups	Diagnosis Prescribing Education	1) *Target beta blocker use: proportion of patients who were initiated or up-titrated on beta-blockers, proportion of patients that	1) *Beta Blocker Use a. Patients initiated or up-titrated on beta-blockers Notification group 16% (10/64) NP facilitator 67% (36/54) Control group 27% (14/51) $p < 0.001$	An independent research assistant assessed the use of beta blocker therapy by reviewing pharmacy records and computerized progress notes in conjunction with

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
To evaluate NP facilitator and combination of patient – specific computer reminders and patient letters, on utilization of beta blocker medications in chronic heart failure (CHF) outpatients, compared to a usual provider education program alone **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment [13]	cardiologists and NPs) were also individually randomized into 3 groups, to decrease the likelihood of contamination, i.e. patients receiving care from their regular providers; median follow-up period = 12 months *Outpatient / Specialized Referral* Academic Medical Centre, San Francisco, California	*Notification Intervention* Internists 10 Cardiologists 2 NPs 3 (n = 64 patients) *NP Facilitator Intervention* Internists 19 Cardiologists 3 NPs 3 (n=54 patients) *Control* Internists 16 Cardiologists 4 NPs 4 (n=51 patients)		reached target dose and were maintained on beta-blockers 2) **Hospitalizations / emergency room visits 3)**Mortality	b. Percent patients to target guideline dose Notification group 2% (1/64) NP facilitator 43% (23/54) Control group 10% (5/51) p < 0.001 c. Mean length of time from initiation to target dose (months) Notification 9.3 NP facilitator 5.9 Control 8.5 p < 0.001 2) **Hospitalizations / emergency room visits Notification 45% (29/64 patients) NP Facilitator 43% (23/54 patients) Control 49% (25/51 patients), p=0.81 3) **Mortality Notification 2% (1/64 patients) NP Facilitator 9% (5/54 patients) Control 14% (7/51 patients), p=0.05 Only 1 death recorded in the notification group eliminates ability to statistically infer impact	patient self-report at 3-month intervals Information on adverse events was collected in this pilot study as an indicator of safety not efficacy (e.g. to confirm no increase in adverse events, versus an efficacious reduction in adverse events)
Hill, 2003 [55] England	RS ^ 12 month study period	80 outpatients, 18 years or older, to rheumatology clinic on at least three previous occasions	Diagnosis Prescribing Clinical Procedures Strategies for	1) *Disease Activity Score results at 24 and 48 weeks past baseline, measured using the DAWN Visual DAS28	1) *Disease Activity Score (DAS28) Week 24: NP 35/39, JHD 34/41 Patients Scores Unchanged: NP 19 JHD 25 Patients Scores Worsened: NP 6 JHD 5 Patients Scores Improved: NP 10 JHD 4 no p-value reported	Per protocol, actual treatment analysis A number of physicians were involved in the study versus only one RNP, resulting in bias

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
To compare the outcome of patients with rheumatoid arthritis (RA) attending a rheumatology NP (RNP) clinic to patients attending the traditional junior hospital doctor's (JHD) clinic **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment [13]	*Outpatient / Specialized Referral* Traditional rheumatology outpatient clinic managed by junior hospital doctors (JHDs) within a large teaching hospital, affiliated with the University of Leeds	*Intervention* = Rheumatology NP (RNP) care (n =39) *Control* = Junior Hospital Doctor (JHD) care (n= 41)	Behaviour Change	calculator 2) **Plasma Viscosity 3) **Pain, physical function and psychological status 4)**Changes to medications, administration of steroid to intra-articular or intra-muscular steroids 5) **Lab tests, investigations 6)**Patient Satisfaction 7) **Patient Knowledge	Week 48: NP 36/39, JHD 35/41 Patients Scores Unchanged: NP 19 JHD 22 Patients Scores Worsened: NP 6 JHD 7 Patients Scores Improved: NP 11 JHD 6 no p-value reported 2) **Plasma Viscosity at 48 weeks Median value (range) RNP 1.62 mPa (1.49– 1.85 mPa) JHD 1.63 mPa (1.50–1.97 mPa) Difference nonsignificant 3) **Pain, physical function, and psychological status a. Week 48 Pain, Median (range) NP 5.7 (2.0 - 9.0); JHD 6.0 (1.5 – 9.5) Difference non-significant b. Week 48 Physical Function Median (range) NP 3.0 (0.8 –8.2); JHD 3.8 (0.4 -7.6) Difference nonsignificant c. Week 48 Length of morning stiffness (minutes), Median (range) NP 60 (0–600); JHD 37.5 (0–270) Difference 22.5 minutes, nonsignificant d. Week 48 Fatigue (minutes) Median value (range) NP 60 (0–600); JHD 270 (0–600) p=0.02 e. Week 48 Psychological status Median (range)	associated with the NP intervention (with one NP, cannot calculate variability through SD, for integration into effect estimate calculations) RNP care may bring benefit to patient for symptom control as per study

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
					NP 2.7 (0.7 – 7.5); JHD 2.5 (0.2 – 6.7) Difference nonsignificant 4) **Changes to medications for symptom control a. NP 24% (56/234); JHD 22% (50/226) Difference 2% non-significant b. Prescriptions for intra-articular / intramuscular corticosteroid injections NP 15% consults (36/234); JHD 13% consults (29/226) Difference 2% non-significant 5) **Lab tests, investigations a. Lab tests NP 5% (11/234 consultations) JHD 10% (23/226 consultations) b. X rays NP 2% (4/234); JHD 3% (7/234) c. GP visits NP 1% (3/234); JHD 5% (12/226) d. Referrals NP 32% (75/234); JHD 12% (26/226) No p-values reported 6) **Patient satisfaction outpatient care at 48 weeks NP scores: baseline 3.57 to 4.1 JHD scores: baseline of 3.60 to 3.56 $p < 0.001$ 7) **Patient knowledge at 48 Weeks No significant differences	
Tranmer, 2004 [46] Canada	IPT ^^ Five week study intervention delivered offsite	200 postoperative cardiac surgery outpatients discharged from first cardiac	Diagnosis Education Care Coordination	1)*Global Quality of Life, using the MOS SF-36 (Medical Outcomes Study Short Form 36)	1) *Mean (SD) Quality of Life at 5 weeks NP 92/102 UC 92/98 patients Physical: NP 36.3 (6.4) UC 36.2 (7.5) Mean difference 0.04 (95% CI -1.99 to 2.08) $p = 0.97$ Mental : NP 50.4 (11.5) UC 51.7 (11.9)	A disease-specific quality of life tool sensitive to nursing interventions may facilitate detection of statistically

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
To determine the effectiveness of NP support on cardiac surgery outpatients during the first five weeks following hospital discharge **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment [13]	via telephone; study patients recruited from hospital prior to discharge *Outpatient / Specialized Referral* Study patients recruited prior to discharge, from teaching hospital affiliated with Queen's University, Kingston, Ontario	surgery with no stay at Intensive Care Unit *Intervention* = Usual Care + NP initiated phone contacts for patients in 1st 5 weeks following hospital discharge (n= 102) *Control* = Usual Care (UC) including education booklet, home-care follow-up as necessary, and NP contact information, with instruction to call with questions or concerns (n= 98)		2) **Postoperative symptom distress 3) **Healthcare Utilization 4) **Patient satisfaction	Mean difference -1.25 (95% CI –4.54 to 2.04) p = 0.45 2) **Mean number (SD) symptoms at 5 weeks Physical NP 3.5 (2.6) UC 3.8 (2.9) p = 0.39 Psychological NP 2.4 (2.1) UC 2.3 (2.2) p = 0.64 Cardiac NP 1.5 (1.1) UC 1.7 (1.1) p = 0.29 Total NP 8.1 (5.0) UC 8.5 (5.5) p = 0.74 3) **Number of self-reported health care contacts at 5 weeks NP 92/102 UC 92/98 patients a. At least one Emergency Room (ER) visit NP 21 UC 15 p = 0.36 b. Unexpected hospital admissions NP 9 UC 8 p = 0.85 c. Home care on discharge NP 27 UC 26 p = 0.88 d. Mean (SD) home care visits NP 11.68 (9.4) UC 10.07 (8.0) p = 0.87 e. Family physician NP 88 UC 86 p = 0.86 f. Specialist NP 50 UC 51 p = 0.88 4) **Patient satisfaction at 5 weeks (scores from a 5-point measurement scale were standardized to scores out of 100) a. Achieving best recovery possible NP 71.3 UC 63.5 p = 0.03 b. Side effect information NP 61.5 UC 54.0 p = 0.05 c. Help with decisions about care	significant differences during early post-operative recovery

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
					NP 66.6 UC 59.0 p = 0.06 d. Knowing what to expect during recovery NP 70.3 UC 65.7 p = 0.23 e. Complication information NP 63.2 UC 56.7 p = 0.11 f. Recognizing potential problems NP 59.6 UC 56.7 p = 0.48 g. Identifying depressive feelings NP 51.0 UC 46.9 p = 0.32 h. Overall Mean (SD) satisfaction with recovery NP 60.5 (20.4) UC 55.7 (20.8) p = 0.08	
Fairall, 2005 [8] South Africa To implement an educational outreach programme for case management of priority respiratory diseases (Practical Approach to Lung Health in South Africa, or PALSA) among adults attending primary care clinics staffed by NPs	IPT ^^ Pragmatic cluster RCT with the primary health care clinic the unit of random allocation Three month study period *Primary Health Care* 40 primary health care clinics in the Free State province	1,999 patients with cough or difficult breathing on presentation or within past 6 months *Intervention* = an educational outreach program (expanded prescribing provisions with locally tailored guidelines) implemented by NPs	Diagnosis Prescribing Strategies for Behaviour Change	1) *Case detection of tuberculosis by sputum microscopy or culture for tuberculosis 2) *Prescriptions for inhaled corticosteroids to treat asthma; antibiotic prescriptions for upper and lower respiratory tract infections	1) *Case detection of tuberculosis (TB) at 3 months Outreach Intervention 6.4% (57/892) Control 3.8% (34/890) OR = 1.72 (95% CI 1.04-2.85) p = 0.04, ICC = 0.007 2) *Prescriptions at 3 months a. Inhaled corticosteroids for asthma Outreach Intervention 13.7% (137/1000) Control 7.7% (77/999) OR = 1.90 (95% CI 1.14 to 3.18) p = 0.006, ICC = 0.019 b. Antibiotics for upper and lower respiratory tract infections Outreach Intervention 39.7% (397/1000) vs Control 39.4% (394/999) OR = 1.01 (95% CI 0.74 to 1.38) p = 0.95, ICC = 0.042	Patients and fieldworkers were blind to intervention status of each clinic; data from patient-held records and records of dispensed drugs, was collected by blinded fieldworkers, with intervention NPs not blinded for obvious reasons While challenges occurred scheduling educational outreach for clinics in small towns and rural areas, educational outreach with integrated case

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
Tertiary Prevention reducing risks / threats to health in long-term chronic illness / permanent impairment [13]	Respiratory Diseases: 1. Tuberculosis 2. Tuberculosis / HIV co-infection 3. Asthma 4. Chronic Obstructive Pulmonary disease (COPD) 5. Upper / lower respiratory tract infection	20 clinics; 1000/1999 patients *Control* = Usual Care, no educational outreach program 20 clinics; 999/1999 patients		3) **Number of HIV patients receiving prescriptions for cotrimoxazole prophylaxis	3) **HIV patients diagnosed with tuberculosis and receiving cotrimoxazole prescription Outreach Intervention 7.8% (13/167) Control 7.5% (11/147) Difference = 0.3% Non-significant	management can improve case detection of TB without extra staff, in resource poor settings as per study
Goessens, 2006 [47] Netherlands To determine whether the extra care of an NP could be beneficial to the cardiovascular risk profile of high–risk patients with manifest vascular disease, at high risk for a new vascular event or death	IPT ^^ Intervention for one year after randomization *Outpatient / Specialized Referral* Risk-factor management clinic in the University Medical Center Utrecht	Cardiovascular disease (CVD) outpatients: Peripheral arterial disease, Abdominal aortic aneurysm, Cerebrovascular disease Coronary heart disease 236 outpatients with two or more	Diagnosis Education At the time of the trial, an NP in the Netherlands was not formally allowed to prescribe; instead, a study	1) *Treatment goals: blood pressure, blood glucose, lipid, homocysteine, BMI (body mass index), and smoking 2) **Self-reported drug utilization	1)*Percentage of patients who achieved treatment goals; mean follow-up of 14 months (range 10-22) a. Low-density lipoprotein (LDL) cholesterol treatment goal < or equal to 3.1 mmol/L NP 88; UC 67 OR = 3.5 (95% CI 1.5–8.6) b. Total cholesterol (mmol/L) treatment goal < 5.0 mmol/L NP 79; UC 61 OR = 3.3 (95% CI 1.5–7.3) c. Systolic blood pressure (mm Hg) treatment goal < 140 mmHg NP 63; UC 37 OR = 2.7 (95% CI 1.3–5.4) d. Body mass index (kg/m^2) treatment goal < 25	Patients were randomized before informed consent was obtained, according to the Zelen design; treatment consent is always sought before actual intervention, Torgerson & Roland (1998) Attrition 31% (71/236) patients: 61 patients gave no informed consent post randomization, including 24 patients randomized to

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Tertiary Prevention reducing risks / threats to health in long-term chronic illness / permanent impairment [13] **Post hoc analysis** **Sol (2008)** *The role of self-efficacy in vascular risk factor management: a randomized controlled trial* **Appendix I-10**		modifiable risk factors: smoking, hypertension, dyslipidemia, diabetes, obesity, hyperhomocysteinemia. *Intervention* = NP at risk factor management clinic + usual care (n=119) *Control* = usual care (UC) by GP & treating vascular specialist (n=117)	physician prescribed or changed medication for patients in the trial	3) **Overall quality of life at one year measured by the medical outcomes study short form 36 (SF-36)	kg/m^2 NP 38; UC 24 OR = 4.0 (95% CI 1.2–13.1) e. Differences non-significant: Diastolic BP, HDL-C, Triglycerides, Fasting Blood Glucose, Homocysteine, Waist Circumference, Smoking 2) **Self-reported drug utilization at mean follow-up of 14 months (range 10 -22 months); no p-values reported a. Lipid-lowering drugs NP 89% (80/90); UC 73% (55/75) b. Glucose-lowering agents NP 19% (17/90); UC 16% (12/75) c. Blood pressure lowering agents NP 77% (69/90); UC 69% (52/75) d. Angiotensin converting enzyme inhibitor/angiotensin II receptor antagonist NP 76% (57/90); UC 53% (40/75) e. Folic acid NP 61% (55/90); UC 28% (21/75) f. Antiplatelet agents NP 90% (81/90); UC 91% (68/75) 3) **Overall quality of life at 1 year Nonsignificant differences between groups	intervention and 37 randomized to control. Another 10 patients did not complete study: 4 patients in each group died during trial, 1 patient moved, and 1 patient developed co-morbidity Management by NP can improve CVD risk factors as per study CVD is globally, the most common cause of morbidity and mortality, influenced by multiple risk factors, such as smoking, obesity, physical inactivity, hypertension, dyslipidemia, and diabetes

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Nathan, 2006 [49] England To evaluate whether follow-up of patients recently discharged from the hospital as a result of acute asthma, can be adequately provided by a respiratory NP compared to a respiratory doctor **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment [13]	RS ^ 6 months study duration post-hospital discharge *Outpatient / Specialized Referral* West Suffolk hospital outpatient clinic	154 outpatients > 16 years of age recently discharged from the hospital as a result of acute asthma *Intervention* = NP care (n= 78) *Control* = Respirologist care (n=76)	Diagnosis Prescribing Education	1) *Number of acute asthma exacerbations within six months of hospital discharge 2) **Peak flow 3) **Disease-specific quality of life (QoL) i) St. George Respiratory Questionnaire (SGRQ) and ii) Asthma Questionnaire 20 (AQ20) 4) **Resource utilization i) hospital readmission ii) outpatient clinic attendance	1) *Number acute asthma exacerbations at 6 months NP 98/174 exacerbations Respirologist 76/174 exacerbations Difference 22 exacerbations p = 0.368 *4 types exacerbations* i) Mean number hospital readmissions per patient NP 0.07 Respirologist 0.18 RR of readmission = 0.40 (95% CI, 0.14 to 1.12) p = 0.09 ii) Emergency nebulization NP 35 times (17 different patients) Respirologist 16 times (10 different patients) no p-value reported iii) Mean number of exacerbations per patient requiring any emergency treatment NP 0.59 Respirologist 0.43 RR= 1.37 (95% CI 0.84 to 2.21) no significant difference (CI contains the null value of 1) iv) IV or oral steroids during exacerbation NP 51.9% (27/52patients) Respirologist 48.1% (25/52 patients) Difference 3.8% p = 0.572 2) **Mean percentage drop (SD) peak flow at 6 months NP 3.92% (12.4) Respirologist 2.53% (11.5) Difference 1.39% (95% CI – 3.84 to 6.63) p= 0.122	Data was collected by an independent research assistant who was unaware of the group to which the patient was allocated No inconsistencies were found between data sources: patient diary card, emergency department attendance records, and general practice records

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					3) **Disease-specific quality of life at 6 months i. St. George's Respiratory Questionnaire (SGRQ) (higher score indicates greater limitations) Mean (SD) percentage reduction, SGRQ score NP 3.94% (14.34) (49/78 patients) Respirologist 5.02% (16.43) (52/76 patients) Difference = 1.08% (95% CI -5.0 to 7.2) p=0.727 ii. Airways Questionnaire 20 (AQ20) (AQ20 high score indicates poor quality of life) Mean (SD) change, AQ20 score NP 0.47 reduction (3.73) (49/70 patients) Respirologist 0.31 increase (3.53) (52/66 patients) Difference 0.78 (95% CI – 0.64 to 2.19) p = 0.285 4) **Resource Utilization i. Mean number hospital readmissions / patient NP 0.07 (5 re-admissions/68 patients) Respirologist 0.18 (12 readmissions/65 patients) RR of readmission = 0.40 (95% CI 0.14 to 1.12) p = 0.09 ii. Mean number follow-up clinics attended NP 1.97 (130 clinics / 66 patients) Respirologist 2.23 (147 clinics / 66 patients) RR = 0.88 (95% CI 0.70 to 1.12) p = 0.011	
McCarrier, 2009 [7] U.S. **Pilot RCT** to assess whether a Web-based	IPT ^^ One year intervention period *Outpatient / Specialized*	78 Type 1 Diabetes Mellitus outpatients, 21 -49 years with at least one A1C test	Diagnosis Education Care Coordination	1) *Difference in mean Hemoglobin A1c between baseline and one year	1) *Mean (SD) change hemoglobin A1c at 1 year NP - 0.37 (1.3) UC: + 0.11 (1.4) Absolute difference = 0.48 (95% CI -1.2 2 to 0.27) p = 0.160	Pilot study with small sample size Attrition at 17% (13/78 patients: 7 patients from UC group, and 6 patients from NP group)

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diabetes case management program based in an electronic medical record accessible to both patient and provider, can improve glycemic control and diabetes-specific self-efficacy in adults with Type I Diabetes Mellitus **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment [13]	*Referral* Diabetes Care Center (DCC: team includes physicians, NPs, on-site pharmacists, nurse educators, nutritionists, and mental health professionals) affiliated with the University of Washington Medical Centre, Seattle, Washington	> or = to 7% in previous 12 months *Intervention* = NP coordination of Web-based care + usual care (n =42) *Control* = usual care (UC) from team at Diabetes Care Center (DCC) (n = 36)		2) **Diabetes-specific self-efficacy	2) **Diabetes-Specific Self-Efficacy at 1 year NP +0.14 (0.62) UC -0.16 (0.62) Effect size = 0.30 (95% CI 0.01 to 0.59) p = 0.044	This study's Web-based case management program is associated with a beneficial treatment effect on self-efficacy, which may improve effectiveness of patients' self-care behaviors
Mitchell, 2009 [54] U.S. To determine the effect of a NP-delivered psychosocial-	IPT ^^ 8 week intervention within a 24 month study period, with follow-ups at 9 & 21 weeks post-entry, and 12 & 24 months post-stroke	101 patients within 4 months of an ischemic stroke and diagnosis of clinical depression *Intervention* = Brief psycho-social/behavioural intervention	Diagnosis Strategies for Behaviour Change	1) *Post-stroke depressive symptomology (reduction in depressive symptoms)	1) *Mean change (SD) Hamilton Rating Scale for Depression (HRSD) at 12 months NP - 9.2 (5.7) 44/48 patients UC: - 6.2 (6.4) 48/53 patients Difference -2.9 (CI -5.4 to -0.4) p=0.023 • Remission (defined as HRSD < or = 9) at 9weeks NP 47% (45/48) UC 19% (53/53)	Family participation (patient support) was not a consistent factor between groups Per protocol analysis Attrition 9% (9/101) of patients were lost to one year follow-up

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behavioural intervention on depression in community dwelling post-stroke patients **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment[13]	*Outpatient / Specialized Referral* Outpatient clinic affiliated with the University of Washington Seattle, Washington; follow-up contact included patients' private homes	(9 in-person sessions with NP over 8 weeks) + usual care, including antidepressant medication (n=48) *Control* = usual care (UC) scheduled by stroke care provider including antidepressant medication (n=53)		2) **Limitations in ability (physical function), participation and overall stroke impact	Difference 28 % OR = 4.8 (CI 1.8 to 12.9) p = 0.001 • Remission at 21weeks NP 46% (46/48) UC 22% (50/53) Difference 24% OR=3.4 (CI 1.3 to 8.7) p = 0.008 • Remission at 12 months NP 48% (44/48); UC 27% (48/53) Difference21% OR=2.7 (CI 1.1 to 6.6) p = 0.031 • Remission at 24 months NP 65% (44/48) UC 46% (48/53) Difference 19% OR =2.3 (CI 0.8 to 6.7) p = 0.130 2) **Measures of overall stroke impact, limitations in physical function, social participation at 12 months, were non-significant	
Ralston, 2009 [6] U.S. To test Web-based management of glycemic control in Type II Diabetes	IPT ^^ 12 month intervention period *Outpatient / Specialized Referral*	83 Type II Diabetes Mellitus outpatients, 18 - 75 years, glycosylated hemoglobin (GHb) in prior year > or = 7%, at least 2 clinic	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	1) *Absolute change in glycated hemoglobin between baseline and end of 12 month study period	1) *Absolute change in glycated hemoglobin at 12 months; target for glycated hemoglobin is < 7% A1C (corresponding to an average blood glucose concentration of less than 8.6 mmol/L) NP 33% at target UC 11% at target Difference = 22% p = 0.03	Incomplete reporting of raw data in Table 3: no fraction of patients comprising percentages reported Patient / provider Web access to same Electronic Medical Record (EMR) can

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Mellitus outpatients, via one NP providing case management services, using a shared electronic medical record **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment [13]	University of Washington General Internal Medicine Clinic (UW GIMC), a teaching clinic that provides care to 7, 707 patients, staffed by 25 faculty, 48 residents, and an NP, for case management of chronic disease patients; Seattle, Washington (Ralston, 2009, p. 234)	visits in prior year *Intervention* = NP coordination of Web-based care + usual care (n=42) *Control* = usual care (UC) from an internal medicine physician (n=41)		2) **Blood pressure, total plasma cholesterol 3) **Healthcare utilization	2) **Mean group difference for change in risk factors • Systolic BP reduction -0.9 mmHg p = 0.84 • Diastolic BP +0.1 mmHg p = 0.96 • Total Cholesterol +0.20 mmol/L p = 0.38 3) **Healthcare Utilization Mean (SD) change in total numbers of visits at 12 months • Outpatient Clinic NP 0.6 (10.7) UC -2.1 (7.0) Difference 2.7 p= 0.18 • Primary Health Care Clinic NP 0.0 (2.9) UC -0.2 (2.8) Difference 0.20 p= 0.76 • Specialty Physician Office NP 0.6 (9.0) UC -1.9 (5.9) Difference 2.5 p= 0.14 • Inpatient Days NP 0.2 (2.6) UC -0.3(1.8) Difference 0.5 p= 0.32	improve glycemic control in type 2 diabetes patients as per study, while single case manager and small sample size limits generalizability
Huizinga, 2010 [51] U.S.	IPT ^^ Two year study intervention delivered offsite via telephone	165 Type II Diabetes Mellitus outpatients, 18-75 years, with recent glycemic control	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	1)*Glycemic relapse	1)*Glycemic relapse, defined as an increase in HbA1c of > or = to 1% over baseline, at 2 years • Quarterly contact 21% (10/48) patients relapsed • Monthly contact 29% (15/52) patients relapsed	Test was performed in a study population already motivated with previous successful glycemic control. Study protocol did not contain care

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To determine the optimal frequency of telephone contact by NPs necessary to prevent glycaemic relapse in Type II Diabetes Mellitus outpatients who had recently achieved glycemic control (≥ 1% decline A1c) **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment[13]	*Outpatient / Specialized Referral* Academic Medical Centre for Diabetes Improvement Program (DIP), offered by a physician-led team, including a NP, registered dietician, and a diabetes nurse; outpatient clinic of Johns Hopkins Hospital, Baltimore, Maryland	*2 Intervention Groups* NP phone contact + Usual Care (UC) : 1) Quarterly contact, every 3 months (n = 55) 2) Monthly contact (n = 55) *Control* = UC in Diabetes Improvement Program (n = 55)			• UC 25% (12/48) patients relapsed p=0.83 Prevalence of relapse did not differ between groups over follow-up time, nor did the cumulative incidence of relapse differ between treatment groups (p = 0.72)	strategies for patients who relapsed, and was not powered for sub-group analysis between its 3 groups
Kim, 2013 [53] South Korea To test the effectiveness of standardized	IPT ^^ Intervention period of 1 week *Outpatient / Specialized Referral*	108 advanced cancer outpatients, 20 - 80 years diagnosed with a stage IV solid tumor, moderate level of cancer-related pain (Visual Analog Scale score ≥4	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	1) *Reduction in average pain levels at 1 week 2) **Performance status / functional impairment; anxiety/ depression,	1)* Reduction in average pain ratings on Brief Pain Inventory at 1 week (0 = no pain; > or = to 4= average pain; 10 = 'pain as bad as you can imagine') Number patients experiencing average pain intensity at 1 week NP 19% (10/54) UC 35% (19/54) Difference 16%	All calculations used actual per protocol data; no adjustments were made for missing data

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education and tele-monitoring (phone contact) for improving pain, distress, anxiety, depression, quality of life, and performance in outpatients with advanced cancer **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment[13]	Severance Hospital Pain Clinic of the Yonsei University Health System, Seoul	out of 10 over last 24 h), and life expectancy > 1 month *Intervention* = usual care + daily phone monitoring by NP (n = 54) *Control* = usual care (UC) of standardized pain education by NP in both study arms at first visit (n = 54)		distress at 1 week 3) **Cancer specific symptoms measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC30)	p = 0.02 2) **Functional impairment, mean (SD) (Karnofsky performance score 100 = 'perfect' health; 0 = death) NP 66 (8.0); UC 65 (9.2) Difference 1 p = 0.68 Percent patients with score ≥ 11, Hospital Anxiety Depression Scale (0 -7=normal, 8-10=borderline abnormal,11-21=abnormal) NP 57% (31/54) UC 54% (29/54) Difference 3% p=0.34 Percent patients ≥ score of 4 on Distress Thermometer (0 = not distressed to 10 = extremely distressed) NP 83% (45/54) UC 91 % (49/54) Difference 8 % p = 0.09 3) **Cancer-specific symptoms (EORTC QLQC30) Physical function, mean (SD) at 1 week (higher scores represent higher levels of functioning) NP 56 (23) UC 55 (21) p = 0.03 Differences in all other component scores were non-significant	

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Sawatsky, 2013 [48] Canada To compare patient outcomes between NP-managed follow-up care and usual follow-up care, for coronary artery bypass graft (CABG) surgery outpatients **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment[13]	IPT ^^ Six week study intervention delivered offsite via telephone *Outpatient / Specialized Referral* Study patients recruited prior to discharge, from St. Boniface Hospital, affiliated with the University of Manitoba, Winnipeg, Manitoba	204 postoperative cardiac surgery outpatients following first time coronary artery bypass graft (CABG) surgery *Intervention* = Usual Care + NP phone contact at 2-3 days post discharge for needs assessment and recommendations: additional NP phone contact, follow-up with primary care provider or cardiac surgeon, NP Follow-Up (NPFU) clinic, or local ED (n= 97)	<u>All 5 domains</u>: Diagnosis Prescribing Clinical Procedures Education Care Coordination	1)*Global quality of life 2) **Symptoms in cardiac surgery recovery 3) **Health resource use 4) **Patient satisfaction	1)* Mean (SD) Global Quality of Life at 2 and 6 weeks post-discharge, SF-36 Physical component 2 weeks NP 19.0 (3.4) UC 18.0 (3.4) p = 0.04 6 weeks NP 22.2 (4.2) UC 22.0 (4.0) p = 0.69 Mental component 2 weeks NP 21.5 (2.1) UC 21.5 (2.3) p = 0.87 6 weeks NP 21.3 (2.3) UC 21.1 (2.3) p = 0.67 2)** Mean (SD) summary symptom-score (including number and frequency of symptoms) 2 weeks NP 45.2 (10.2) UC 50.4 (12.6) Difference 5.2 p = 0.002 6 weeks NP 41.2 (11.1) UC 43.2 (11.1) Difference 2.0 p = 0.23 Palpitations and leg pain were reported with less frequency in NP group vs UC at 6 weeks post-discharge ($p < 0.05$) no individual data shown 3)** Health care resources utilization at 6 weeks a. Total emergency department (ED) visits NP 30 UC 37 Difference 7 visits b. Total medical doctor (MD) visits	Disruption of randomized sample: once intervention was established, several control patients were pulled from the trial, deemed too ill for the study (Sawatsky, 2013, p. 2085)

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		Control = Usual Care (UC) including advice to make primary care provider appointment within 1 week; return visit to cardiac surgeon was scheduled for all patients at 6 weeks (n=107)			NP 208 UC 210 Difference 2 visits c. Total hospitalizations NP 15 UC 19 Difference 4 hospitalizations 4)**Patient satisfaction NP intervention patients were significantly more satisfied a. Quality of Service at 2 and 6 weeks respectively: p = 0.003 and 0.005 b. Amount of Help Received at 2 and 6 weeks respectively: p = 0.001 and 0.002 (no individual data shown)	
Berkhof, 2014 [50] Netherlands **Pilot RCT** to assess the effect of an on-demand system of patient-initiated outpatient visits on health status for patients with Chronic Obstructive Pulmonary Disease	IPT ^^ 2 year study *Outpatient / Specialized Referral* Large teaching hospital, Zwolle	100 Chronic Obstructive Pulmonary Disease (COPD) outpatients > or = to 40 years, COPD GOLD stage > or = to 2 (Global initiative for staging Obstructive Lung Disease: 1 = mild;	Diagnosis Prescribing Education	1) *Mean change in Clinical COPD Questionnaire, or CCQ (an increase in total score indicates a decline in health status) 2) **Time to first exacerbation COPD	1) *****Mean (SE) change COPD (Chronic Obstructive Pulmonary Disease) status at 2 years Lower score on Clinical COPD Questionnaire (CCQ) = less deterioration / better health status Minimal clinically important difference (MCID) of CCQ total score is 0.4 Symptom domain of the CCQ NP 0.14 (+ or - 0.14) in 40/49 patients UC 0.58 (+ or - 0.16) in 29/51 patients Difference = - 0.44 (+ or - 0.21) 95% CI -0.87 to -0.023, p = 0.04 Absolute difference between groups of 0.44 met the MCID for a clinically relevant effect	Results of this pilot study are exploratory: the on-demand system of patient scheduling had not been investigated before in COPD patients Less deterioration in COPD health status for intervention patients was not accompanied by significant

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(COPD) a progressive disease **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment[13] *Feb. 17, 2017* €1.00 Euro = $1.53 Canadian €0.72 Euro = $1.00 Canadian		4 = very severe) smoking history >10 pack-years *Intervention* = patient-initiated outpatient visits with pulmonary NP upon increase of symptoms (dyspnea, cough, sputum, hemoptysis, or thoracic pain); NP followed an 'on-demand protocol' that included consult with pulmonologist for urgent problems (n =49) *Control*= usual care (UC) of traditional outpatient visits initiated by pulmonologist,		3) **Visits to general practice physicians, pulmonologists, and pulmonary NPs 4) **Total treatment costs from provider and insurance perspectives 5) **Disease-specific quality of life measured by St. George's Respiratory Questionnaire 6) **Global quality of life measured by the Short Form-36 (SF-36)	2) **Median time to 1st exacerbation COPD at 2 years NP 307 days + or - 61.6 days (95% CI 186.3 to 427.7) UC 335 days + or - 60.2 days (95% CI 217.0 to 453.0) Difference 28 days p=0.40 3)**Healthcare Visits median scores (range) at 2 years • Primary Health Care GP Intervention 4 (0-32); Control 5 (0-20) p = 0.01 • Outpatient Pulmonary NP Intervention 1 (0-14); Control 0 (0-4) p = 0.003 • Pulmonologist Intervention 3 (0-17); Control 3 (0-13), p = 0.82 4) **Total HC provider costs at 2 years, mean (SD) Intervention €1803 (€2617); Control €2321 (€3967) Difference € -518 (CI -€1993; €788), nonsignificant Total HC insurance costs at 2 years, mean (SD) Intervention €3994 (€4669); Control €4452 (€ 6100) Difference -€458 (CI -€2700,€ 1652), nonsignificant 5) **St. George's Respiratory Questionnaire (SGRQ) mean (SE) symptom domain at 2 years (higher score = worse health status; minimal clinically important difference (MCID) of SGRQ total score is 4)	differences in overall/global quality of life measures (SF-36)

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		to the pulmonologist or the pulmonary NP (n=51)			NP 2.6 (3.0) 38/49 patients UC 10.3 (3.4) 30/51patients Difference 7.7 (4.6) 95% CI -16.8 to 1.4 p = 0.10, meeting MCID for a clinically relevant effect 6) **Overall quality of life at two years No significant differences between groups; 3/8 component scores on SF-36 met the minimal clinically important difference (MCID)	
Mertens, 2014 [68] South Africa To assess the effectiveness of a brief motivational interviewing intervention for alcohol & drug use in young adult primary care patients of low socioeconomic status **Tertiary Prevention** reducing risks / threats to health in long-term chronic illness / permanent impairment[13]	IPT ^^ Study period 3 months *Primary Health Care* Large public sector primary healthcare clinic in Delft, a township in the Western Cape	403 primary health care clinic patients 18–24 years who screened for high-risk alcohol and / or drug use *Intervention* = single session of Brief Motivational Interviewing (average session 10 minutes) delivered by NP + referral list of resources (n=206)	<u>Only 1domain:</u> Strategies for Behaviour Change	1)*Rates of at-risk alcohol use and drug use at three month follow-up	1) *****Mean % reduction in ASSIST scores at 3 months (ASSIST - Alcohol, Smoking and Substance Involvement Screening Test) • Alcohol NP 38.3 % Control 20.9% p = 0.0293 • Cannabis NP 28.3% Control 9.8% p = 0.1119 • Methamphetamine NP 57.2% Control 76.9% p = 0.2264	Raw data in Table 2 incomplete: no fraction of patients comprising percentages was reported Attrition 40/403 = 10% A brief motivational interviewing intervention delivered by NPs may reduce at-risk (medium to high risk scores on the ASSIST instrument) alcohol use, the most prevalent substance used, in the short term among

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		Control = minimally enhanced usual care & referral list of resources (n=197)				economically disadvantaged young adults, as per study
Ganz, 2000 [61] U.S. To test the effect of a comprehensive menopausal assessment intervention program in breast cancer survivors, for their achievement of relief in abruptly recurred menopausal symptoms, improvement in quality of life, and sexual functioning at four months	IPT ^^ Intervention period of 4 months *Outpatient / Specialized Referral* Outpatient clinic at the Jonsson Comprehensive Cancer Center, University of California, Los Angeles, California	76 surviving breast cancer outpatients with abruptly recurred menopause symptoms due to discontinued estrogen replacement therapy (ERT) related to breast cancer *Intervention* = comprehensive menopausal assessment or CMA (targets highly symptomatic women with goal of reducing	Diagnosis Prescribing Strategies for Behaviour Change	1) *Composite menopausal symptom scale for abruptly recurred menopause symptoms due to discontinued estrogen replacement therapy, related to breast cancer 2) **Vitality, from Medical Outcomes Study Short Form 36 (SF-36) 3) **Cancer Rehabilitation	1) *Menopause symptom-scale score, mean change (reduction) from baseline to 4 months NP 0.61 (95% CI 0.40–0.82), 33/37 patients UC 0.19 (95% CI −0.06 to 0.44) 39/39 patients p = 0.0004 2) **Vitality, at baseline and 4 months Vitality, a dimension of health-related quality of life on the SF-36 tool p = 0 .77 3) **Sexual functioning scale (Cancer Rehabilitation	Potential side effects to clonidine (fatigue, headache) used to treat ‘hot flashes’ in 39% of the intervention patients, may have limited detection of intervention effect on SF-36 Vitality Scale Instead of using intention to treat analysis, estimation of intervention efficacy was made according to methods described by Angrist JD, Imbens GW, Rubin DB. *Identification of causal effects using*

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Secondary Prevention reducing risks / threats to health in a condition that has already occurred to halt or slow progress[13]		symptoms) delivered by NP (n=37) *Control* = usual care (UC) +1 contact from research assistant at 2 months asking of therapies used for symptom management (n= 39)		Evaluation System (CARES) Sexual Functioning Scale	Evaluation System, CARES) mean change from baseline to 4 months NP 0.38 (95% CI 0.05–0.71) 33/37 patients UC 0.015 (95% CI −0.37 to 0.40) 39/39 patients p = 0.04	*instrumental variables*. J Am Stat Assoc 1996, (p. 1056)
Cooper, 2002 [62] Scotland To develop methods and tools that could be easily used in different emergency departments, for evaluation of emergency NP care	RS ^ 2 month study duration *Acute Care Emergency Department*	204 patients over 16 years, with minor injury that fell within the emergency NP (ENP) protocol *Intervention* = ENP-led care (n = 102)	Diagnosis Prescribing Clinical Procedures Education	1) Resource Utilization: consultation time and referral to follow-up clinics 2) Unplanned Follow-up 3) Missed Injuries	*Endpoints not pre-specified as primary / secondary* 1) Resource Utilization Patient's average wait time ENP 48.6 minutes SHO 70.1 minutes 95% CI 11.2–31.8 minutes, p < 0.001 Total consult time (including treatment time) ENP 30.0 minutes SHO 24.9 minutes 95% CI -1.3 to 11.5 minutes, p < 0.115 Seeking advice from senior medical staff (when X-ray interpretation was excluded: ENPs were required to consult while SHOs were not required to consult) ENP 20.9% SHO 11.5%, p < 0.21	Wait time and consult time data were based on use of the 'Treatment Record' form for consultations and referrals; returns to the emergency department by study patients and missed injuries, were tracked by the hospital computer system

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Secondary Prevention reducing risks / threats to health in a condition that has already occurred to halt or slow progress[13]	Single Accident and Emergency (A & E) Department of Glasgow Royal Infirmary, Glasgow	*Control* = Senior House Officer (SHOs)-led care (n = 102)		4) Patient Satisfaction 5) Quality of Clinical Documentation 6) Recovery at one month	Numbers of X-rays requested ENP 56.6% SHO 47.5%, p = 0.2 Referral to follow-up clinics ENP 33.3 % SHO 27.5%, p = 0.358 2) Reasons for unplanned return regarding 6/10 NP patients and 4/10 SHO patients: • New injuries ENP 1 SHO 1 • Concern about original injury ENP 2 SHO 1 • Problems complying with treatment ENP 2 SHO 1 • Problems with treatment ENP 1 SHO 1 3) Missed injuries ENP 1 SHO 1 4) Patient Satisfaction a. Patients reported it was easier to talk to ENPs NP 97.6 (85/102) SHO 84.0 (81/102) p = 0.009 b. Patients were given information on accident and illness prevention NP 75.3 (81/102) SHO 45.2 (73/102) p =0.001 c. Patients were given enough information on their injury NP 95.2 (83/102) SHO 82.5 (80/102)	Inherent to all self-completion questionnaires: 1) Refusal to complete/return the questionnaire, leading to bias if non-responders differ from responders 2) Patients may ask other people to assist in completing the questionnaire, or even complete it on their behalf, prejudicing the sample 3) Lack of ability to read (low literacy levels / illiteracy in patients) may contribute to non-response

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					p = 0.007 d. Overall patient satisfaction NP 98.8 (85/102) SHO 87.7 (81/102), p < 0.001 e. Between-group differences in remaining 4 satisfaction statements were non-significant (see Appendix I-9) 5) Quality of Clinical Documentation, scored out of 30, audited 4 months after the trial ended ENP 28.0/30 (94/102) SHO 26.6 /30 (92/102) p < 0.001 6) Recovery at one month: symptoms and 'level of activity' all non-significant (no individual data shown)	
Williams, 2005 [60] England To evaluate the impact of a service led by a continence NP (designed for this	IPT ^^ Six month intervention period *Primary Health Care* Patients' homes in Leicestershire and Rutland	3746 patients aged 40 years and over living in private households, with incontinence several times per month or more, or several times a year, and reported impact of symptoms on quality of life	Diagnosis Prescribing Education	1) *Improvement in one or more symptoms (incontinence, urgency, frequency, and nocturia), of which cure (no symptoms) is a subset	1) *Improvement in 1 or more symptoms 3 months NP 60% (1417/ 2378 responders) Control 48% (281/584 responders) Difference 12% (95% CI 7 to 16) p < 0.001 6 months NP 62% (1369/2201 responders) Control 52% (277/536 responders) Difference 10% (95% CI 6 to 15) p < 0.001 Cure = 0 symptoms 3 months NP 25% (591/2378) Control 15% (88/584)	Incomplete reporting: Cost data represents only 24% (905/3746) of all study patients; 19% (171/905) control patients; 81% intervention patients 734/905. Seventy-six percent of the entire study population were not included in the cost-effectiveness analysis (CEA)

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study) compared to existing primary / secondary care for people with urinary incontinence and storage symptoms **Secondary Prevention** reducing risks / threats to health in a condition that has already occurred to halt or slow progress[13] **Post hoc analysis Williams (2011)** *Long term follow-up of a randomised controlled trial of services for urinary symptoms* **Appendices I-3, I-7**		*Intervention* = continence service provided by NPs (n = 2958) *Control* = existing usual primary care including GP and continence advisory services (n = 788) 4:1 ratio was deemed necessary to ensure sufficient intervention data for evaluation of detrusor muscle over-activity (bladder wall) and urodynamic stress incontinence		2)**Number of symptoms alleviated 3) **Resources measured healthcare professional contacts, investigations; Cost-effectiveness 4) **Patient satisfaction and patient perception of problem	Difference 10% (95% CI 6 to 13) $p < 0.001$ 6 months NP 28% (624/ 2201) Control 19% (104/536) Difference 9% (95% CI 5 to 13) $p < 0.001$ 2)**Number of symptoms alleviated At 3 and 6 month time points, the percentage of responders reporting each of all four symptoms /events were statistically significantly less in the intervention group than control, with the exception of one borderline result at p=0.066 Differences ranged from 11% $p < 0.001$ to 4% $p = 0.066$ 3) **Cost-effectiveness according to number of symptoms alleviated, at 6 months In the 3rd- 6th months of study, costs generated by the NP service were similar to months 1-3, while the overall difference in mean number of symptoms alleviated remained the same, resulting in an incremental cost / additional symptom alleviated that was greater at 6 months (£488) than at 3 months (£242), no p-values reported Higher start-up costs/longer consults limited cost-effectiveness of intervention	Inconclusive, related to: 1) Inconsistent sourcing of data upon which CEA was based, integrating published cost data for control, and only using data estimates not similarly verifiable, for intervention cost 2) No comparative resource data or associated stratified cost comprising the CEA numbers for the reader to critically appraise

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Feb.17, 2017 £ 1.00 Great Britain = $1.62 Canadian £ 0.62 Great Britain = $1.00 Canadian					4) **Patient Satisfaction a. 3 months NP 52% (1294/2498) Control 45% (276/618) Difference 7% (95% CI 3 to 12) p = 0.001 b. 6 months NP 64% (1428/2236) Control 53% (289/546) Difference 11% (95% CI 6 to 16) p <0.001 Patient Perception of Problem as Mild or None a. 3 months NP 74% (819/2468) Control 68% (416/614) Difference 6% (95% CI 2 to 10) p = 0.003 b. 6 months NP 79% (1721/2181) Control 70% (380/545) Difference 9% (95% CI 5 to 13) p <0.001	
Krichbaum, 2007 [64] U.S. **Pilot RCT** to test the effectiveness of a nursing intervention	IPT ^^ Six month intervention in a 12 month study period *Outpatient / Specialized*	33 hip fracture surgery outpatients at least 65 years, admitted from home or assisted living facilities, and ambulatory prior to	Diagnosis Prescribing (medication reconciliation) Strategies for Behaviour Change	1) Self-rated health 2) Level of geriatric depression 3) Activities of daily living or ADLs: basic	*Endpoints not pre-specified as primary / secondary* Mean (SD) symptoms / function at 12 months 1) Self-rated health (Global Health (GH) self-ratings - higher scores better) NP 4.1 (0.95) Control 4.0 (0.71) Difference non-significant	Findings provide effect sizes that may be useful in designing larger studies for further tests of the Post-Acute Care Coordination (PACC) model on older adults recovering from hip

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model: the Post-Acute Care Coordination (PACC) model, for improvement in health, function, and return-home outcomes in elders with hip fracture **Secondary Prevention** reducing risks / threats to health in a condition that has already occurred to halt or slow progress[13]	*Referral* Patients were recruited from two hospitals in St. Paul, Minnesota Mobile NP followed the patient to all discharge locations, including subacute care facilities, long term care facilities, rehabilitation agencies, and private homes	hip fracture *Intervention* = usual care + post-acute care coordination by gerontologic NP with experience in orthopedics (n=17) *Control* = usual care according to hospital and individual surgeon's protocols for the post-acute care period (n=16)		self-care tasks, skills usually learned in early childhood, and instrumental activities of daily living or IADLs: complex skills needed to successfully live independently, usually learned during teenage years, measured by the Functional Status Index	2) Depression (Geriatric Depression Scale - higher scores worse) NP 2.2 (2.4) Control 1.7 (1.7) Difference non-significant 3) Activities of daily living (ADLs higher scores worse) • Mobility NP 1.42 (0.48) Control 1.24 (0.34) • Personal care NP 1.22 (0.32) Control 1.41 (0.53) Differences non-significant Instrumental ADLs (IADL) (higher scores worse) • Home chores NP 1.44 (0.19) Control 1.48 (0.51) • Social NP 1.54 (0.61) Control 1.39 (0.49) Differences non-significant	fracture surgery High attrition (30%; 10/33) on a very small sample: 4 patients withdrew: 3 control and 1 intervention 6 patients died: 3 from each group - 3 to cancer, 1 from myocardial infarction, 1 from stroke, and 1 from post-operative complication
Dierick-van Daele, 2009 [67] Netherlands To evaluate process and outcomes of care provided to patients	RS ^ Two week intervention within a study duration of 6 months	1,591 primary health care (PHC) patients 16 years and older, with common complaints regarding	Diagnosis Prescribing Education	1) Duration of consultation 2) Medical resource use 3) Number of prescriptions	*Endpoints not pre-specified as primary / secondary* 1) Mean (SD) duration of consultation (minutes) NP 12.22 (5.7 minutes) GP 9.20 (4.8 minutes) $p < 0.001$ 2) Medical resource use • Investigations	No psychometric properties information for study questionnaires, but only a justification of validity according to study authors' assurance on

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
with common complaints by GPs or specially trained NPs as first point of contact in primary health care clinics in the Netherlands **Secondary Prevention** reducing risks / threats to health in a condition that has already occurred to halt or slow progress[13] **Post hoc analysis Dierick-van Daele (2010)** *Economic evaluation of nurse practitioners vs GPs in treating common conditions* **Appendix I-7**	*Primary Health Care* Trial affiliated with the School of Primary Care and Public Health, University of Maastricht; Foundation for Development of Quality Care in General Practice, Eindhoven Patients who attended a general practice on a day when the NP was present were invited to participate in the trial that ran in 15 general practices Study practices were also	respiratory/ throat, ear/nose musculoskeletal /skin injuries, urinary/ gynaecological and geriatric problems *Intervention* = patient care from newly graduated NP (Master Degree of Advanced Nursing Practice), experience ranging from 1 to 5 years 12 NPs (n = 817) *Control* = patient care from GP with an average of 16 years' experience		given 4) Patient satisfaction and patient perceptions of quality of care	NP 2.4% (18/747) GP 2.9% (19/650) p = 0.55 • Referrals NP 12 % (90/747) GP 14.2 % (92/650) p =0.24 • Asked to return NP 50.3% (340/676) GP 41.3% (250/604) p = 0.001 • Returned for same continuing problem NP 23.5% (121/515) GP 18.3% (89/487) p = 0.040 • Mean (SD) length of absence from paid job due to illness (days) NP 1.11 (0.32) GP 1.11 (0.31) 3) Numbers of prescriptions given • One prescription NP 55.0% (411/747) GP 54.2% (352/650) Difference 0.8%, p = 0.75 • Two prescriptions NP 16.9% (126/747) GP 19.5 % (127/650) Difference 2.6%, p = 0.20 • Three or more prescriptions NP 8.8% (66/747) GP 7.8% (51/650) Difference 1.0%, p = 0.51 4) Mean (SD) patient satisfaction and patient perceptions of quality of care • Patient satisfaction for patients in NP group who reported at least one chronic disease	discussion with 2 GPs with research experience. The questionnaires were next tested on a group of 40 patients, resulting in two textual refinements as well as "asking the name of the practitioner instead of type of practitioner (NP or GP) consulted." Baseline differences in study design included a booking time set at 15 minutes for NPs versus 10 minutes set for GPs

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Feb. 17, 2017 €1.00 Euro = $1.53 Canadian €0.72 Euro = $1.00 Canadian	compared to external reference practices where 17 GPs worked in 5 general practices without involvement of NPs	50 GPs (n = 684)			(583/1591patients) NP 8.35 (1.07) UC 8.11 (1.32) p = 0.02 All other patient satisfaction measures were non-significant • Patient perceptions of quality of care at 6 months NP 8.19 (1.18) GP 8.20 (1.26) p= 0.83	
McCorkle, 2009[52] U.S. To evaluate the effectiveness of an intervention provided by an oncology NP and a psychiatric liaison NP on women post-surgery for suspected diagnosis of ovarian cancer, for cancer-specific and global quality of life (QOL) outcomes, compared to an attention control	IPT ^^ Six month study duration *Outpatient / Specialized Referral* Patient contact made at private homes or by telephone, northeast Connecticut Trial approved by Yale University, New Haven, Connecticut	149 female outpatients with suspected primary diagnosis of ovarian cancer after abdominal surgery; 21 years or older, with prognosis of at least 6 months and an order to initiate chemotherapy *Intervention* = 18 contacts by an oncology NP, supported by psychiatric	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	*Quality of Life (QOL) <u>1. Cancer specific</u> a) Center for Epidemiological Studies-Depression (CES-D) (total score range 0 to 60; score > or = to 16 indicates impairment) b) Ambiguity subscale of the Mishel 'Uncertainty in	*QOL was measured at baseline (24–48 hours after surgery) 1, 3, and 6 months post-surgery Adjusted QOL baseline scores were included as covariates in **3 types of mixed effect regression models,** built to estimate 'rates of change' (effect estimates) in different QOL measures over time: **(1) Oncology NP intervention without PSYNP** - Rate of reduction in MUIS score was significantly greater for intervention vs control <u>Uncertainty of Illness (MUIS)</u> effect estimate = - 0.04847 ± se 0.01394, p = 0.0006 - Rate of change in CES-D, SDS and SF-12 physical scores was significantly greater for control vs intervention <u>CES-Depression (CES-D)</u> effect estimate = 0.06566 ± se 0.02190, p = 0.0030 <u>Symptom Distress Scale (SDS)</u> effect estimate = 0.05092 ± se 0.01638, p = 0.0021 <u>SF-12 physical component</u>	Baseline measures were obtained prior to randomization, with significant differences found in three out of five QOL scores, and lower baseline QOL in the NP intervention group Baseline QOL scores were adjusted for model testing, with final covariates including age, marital status, number of comorbidities, disease status (recurrence or not),

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Secondary Prevention reducing risks / threats to health in a condition that has already occurred to halt or slow progress;[13] without a definitive diagnosis of ovarian cancer (only suspected), this study is classified as secondary prevention with regards to ovarian cancer, the study's target disease **Post hoc analysis McCorkle (2011)** *Healthcare utilization in women after abdominal surgery for ovarian cancer* **Appendix I-6**	Variable within intervention = use of psychiatric NP (PSYNP) when high emotional distress (Distress Thermometer > or = to 4)	NP (PSYNP) consults (32/74 intervention patients) when warranted for high emotional distress = Distress Thermometer > or = to 4 (n=74) *Attention Control* = nine contacts by research assistant, supported by medical social worker (no data for patient contact with social worker) (n = 75)		Illness' Scale (MUIS) (scores range 13 to 65; higher scores, more uncertainty) c) Symptom Distress Scale (SDS) (rated from 1to 5; :1 indicates absence/low symptoms & 5 indicates high symptom severity) <u>2. Overall / Global (non-cancer specific) Quality of Life (QOL)</u> a) SF-12 physical component b) SF-12 mental component	effect estimate = - 0.07599 ± se 0.02425, p = 0.0019 - Non-significant rate of increase in global, mental QOL for intervention vs control <u>SF-12 mental component</u> effect estimate = 0.01776 ± se 0.01138, p = 0.1195 **(2) Oncology NP intervention with PSYNP** • Rate of reduction in MUIS score & rate of improvement in the SF-12 score was significantly greater for intervention vs control <u>Uncertainty of Illness (MUIS)</u> effect estimate = - 0.03917 ± se 0.00915, p < 0.0001 <u>SF-12 mental component</u> effect estimate = 0.02300 ± se 0.00748, p = 0.0023 • Rate of change in CES-D scores was significantly greater for control vs intervention <u>CES-Depression (CES-D)</u> effect estimate = 0.03594 ± se 0.01213, p = 0.0033 • Poor model fit - no effect estimate data for SDS or SF-12 physical <u>Symptom Distress Scale (SDS)</u> <u>SF-12 physical component</u> **(3) PSYNP separate from Oncology NP** The PSYNP component significantly increased the rate of improvement over time in all QOL measures except for the CES-D	and education level Cancer care that addresses both physical and emotional QOL in synchrony, may contribute to enhanced rate of improvement in QOL as per study

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					<u>Uncertainty of Illness (MUIS)</u> effect estimate = - 0.04978 ± se 0.02094, p = 0.0181 <u>Symptom Distress Scale (SDS)</u> effect estimate = - 0.1164 ± se 0.01284, p < 0.0001 <u>SF-12-mental component</u> effect estimate = 0.06558 ± se 0.01676, p = 0.0001 <u>SF-12-physical component</u> effect estimate = 0.1948 ± se 0.03877, p < 0.0001 -Non-significant rate of change greater for control vs intervention <u>CES-Depression (CES-D)</u> effect estimate = 0.01662 ± se 0.03549, p = 0.6400	
ter Bogt, 2009 [56] Netherlands To investigate the long-term effects of lifestyle counseling by NPs, and its potential contribution to counteracting rising trends of overweight/obesity Hypothesis -an early	RS ^ One year duration to the Groningen Overweight and Lifestyle (GOAL) study, Groningen *Primary Health Care*	457 Primary Health Care patients with BMI 25- 40, and either hypertension, dyslipidemia or both *Intervention* = low-intensity (for prevention of additional weight gain) lifestyle counseling by NPs over one	Diagnosis Prescribing Strategies for Behaviour Change Care Coordination	1) *Changes in body weight after one year of intervention 2) **Waist circumference	1) *****Percentage change in body weight at 1 year NP -1.9% (95% CI -2.5, -1.2) 200/225 patients UC -0.9% (95% CI -1.5, -0.2) 214/232 patients Difference 1.0%, p < 0.05 Weight losers (successful) and stabilizers (percentage of subjects who gained less than 1% body weight by end of study) at 1 year • Women NP 72.8% (75/103) patients GP 64.0% (73/114) patients Difference 8.8% non-significant • Men NP 80.6% (79/98) patients GP 65.3% (66/101) patients Difference 15.3%, p <0.05	Attrition 9% (41/457); 24 intervention patients + 17 control patients General linear model showed that gender is an effect modifier; data thus reported separately for men & women

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focus on preventing progression of overweight /comorbidities through weight stabilization, versus weight loss, may be more successful in the long term. **Secondary Prevention** reducing risks / threats to health in a condition that has already occurred to halt or slow progress;[13] although obesity is now considered a chronic disease, it is reversible, thus secondary prevention	11 general practice locations (1-7 GPs and 1-3 NPs per location), Groningen, northern Netherlands Obesity: Body Mass Index (BMI) > or = 30 kg/m^2 Moderately Overweight: BMI = 25 - 30 kg/m^2	year: 4 individual visits and 1 feedback session by telephone (n =225) *Control* = usual primary health care (PHC) from GPs (n = 232)		3) **Blood pressure, total cholesterol, and fasting glucose one year after intervention	2) **Mean (SD) waist circumference at 1 year • Women NP -2.0 cm (7.8) on 103/225 female patients GP -1.5 cm (6.8) on 114/232 female patients Difference 0.5 cm non-significant • Men NP -2.8 cm (6.2) on 98/225 male patients GP -0.9 cm (4.5) on 101/232 male patients Difference 1.9 cm, $p < 0.05$ 3) **Blood pressure, total cholesterol, and fasting glucose one year after intervention a. Systolic blood pressure (SBP) reduction in obese men (BMI > or = 30 kg/m^2) NP -14 mmHg; UC -5 mmHg Difference = 9 mmHg reduction $p < 0.05$ b. Systolic blood pressure (SBP), mean reduction (SD) • Men (BMI 25 - 40 kg/m^2) NP -8.5 (16.8) mmHg UC -5.3 (12.7) mmHg Difference = 3.2 mmHg reduction non-significant • Women (BMI 25 -40 kg/m^2) NP -5.3 (20.1) mmHg UC -2.2(16.5) mmHg Difference = 3.1 mmHg reduction non-significant	

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Post hoc analysis ter Bogt (2011) Preventing Weight Gain by Lifestyle Intervention in a General Practice Setting *Three-Year Results of a Randomized Controlled Trial*, American Medical Association **Appendices I-2, I-3**	**Post hoc analysis ter Bogt (2011)** *Changes in lifestyle habits after counselling by nurse practitioners: 1-year results of the Groningen Overweight and Lifestyle study*, Public Health Nutrition **Appendix I-3**	**Post hoc analysis Driehuis (2012)** *Maintenance of lifestyle changes: 3-Year results of the Groningen Overweight and Lifestyle study*, Patient Education and Counselling **Appendix I-3**			c. Total cholesterol, mean change (SD) Women & Men (BMI 25 -40 kg/m^2) Between group differences non-significant d. Fasting Glucose, mean reduction (SD) Women & Men (BMI 25 -40 kg/m^2) Between group differences non-significant	
Schuttelaar, 2010 [59] Netherlands To compare the level of care by NPs with that by dermatologists in children with atopic dermatitis (eczema) **Secondary Prevention** reducing risks / threats to health in a condition that has	RS ^ 1 year study *Outpatient / Specialized Referral* Dermatology outpatient clinic of the University Medical Center in Groningen	160 patients < 16 years: 80 patients < or = to 4 years & 80 patients 4–16 years, all new referrals from GPs or pediatricians with a diagnosis of eczema *Intervention* = NP-led care (n=81)	Diagnosis Prescribing Strategies for Behaviour Change	1) *Change in quality of life of the child at 12 months measured by the Infants' Dermatitis Quality of Life Index for children aged < or = to 4 years or by the illustrated version of the Children's	1) *Eczema-specific Quality of Life (higher scores representing a poor quality of life) at 12 months • Infants' Dermatitis Quality of Life Index, mean (SD) NP 5.7 (5.4); Dermatologist 5.6 (3.9), p= 0.26 • Children's Dermatology Life Quality Index, mean (SD) NP 4.9 (3.5), Dermatologist 5.6 (4.2), p= 0.55 2) **Eczema severity at 12 months, mean (SD) NP 13.2 (16.6) (73/81) Dermatologist 13.1 (17.1) (70/79)	Intervention treatment primarily carried out by one NP in single dermatology outpatient clinic The impact of pediatric eczema on family may be similarly managed by NP care as by dermatologist care as per study, in a patient population that was

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already occurred to halt or slow progress[13] **Post hoc analysis Schuttelaar (2011)** *Costs and cost-effectiveness analysis of treatment in children with eczema by NP vs dermatologist: results of a randomized, controlled trial and a review of international costs* **Appendix I-6**	*Feb. 17, 2017* €1.00 Euro = $1.53 Canadian €0.72 Euro = $1.00 Canadian	Age < or = to 4 years (n=40) Age 4-16 years (n=41) *Control* = conventional care by dermatologist (n =79) Age < or = to 4 years (n=40) Age 4-16 years (n=39)		Dermatology of Life Quality Index for children aged 4–16 years 2) **Eczema severity 3) **Family impact of childhood eczema 4) **Patient satisfaction at 4, 8, and 12 months	Difference was reported as 0.2 (95% CI 5.4 to 5.7) p = 0.9 3) **Family Impact of childhood eczema Between groups differences were not statistically significant at baseline, 4, 8, or 12 months, nor for groups stratified by age of children 4) **Patient satisfaction at 4, 8, and 12 months, mean scores (SD) • 4 months NP 27.1 (3.9); Control 24.4 (3.4), p < 0.001 • 8 months NP 27.3 (4.0); Control 24.3 (3.3), p < 0.001 • 12 months NP 26.9 (4.9); Control 24.8 (4.3), p < 0.023	representative of normal referrals from GP to specialist care
Enguidanos, 2012[65] U.S. **Pilot RCT** to assess whether a 'Brief NP Transition' (BNPT) intervention could improve patient self-efficacy and patient satisfaction, as well as reduce medical service use among	IPT ^^ 6 month study duration *Outpatient / Specialized Referral* Set in a managed	199 at-risk hospitalized older adults discharged home without in-home care (e.g. home health/hospice) or caregivers; recruited from hospital prior to discharge *Intervention* =	Diagnosis Prescribing (medication reconciliation) Education Care Coordination	1) Efficacy in Self-Care 2) Home Care Patient Satisfaction Measure	*Endpoints not pre-specified as primary / secondary* 1) Efficacy in Self-Care at 6 months No significant differences between groups 2) Patient satisfaction at 3 months No significant differences between groups	Attrition on follow-up surveys resulted in a 65% response rate, limiting detection of between-groups differences NP support on transition from hospital to home, during a high-risk period for older

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hospitalized older adults discharged to home, who do not qualify for home health care services, hospice, or palliative care **Secondary Prevention** reducing risks / threats to health in a condition that has already occurred to halt or slow progress[13]	care medical center, or Health Maintenance Organization (HMO), Los Angeles County, California	Brief NP Transition, a 'bridge' of up to 3 home visits, 2 phone calls from primary health care NP, within 72 hours of discharge (n = 100) *Control* = standard medical care, including access to case management services (wait time 2-14 days) (n =99)		3) Emergency room visits, hospital re-admission, days re-hospitalized, number of physician office visits, and home health care days	3) Mean (SD) Resource Utilization at 6 months Emergency room visits NP 0.50 (1.2) Control 0.99 (2.5) p =0.096 Hospital re-admission rate NP 40% Control 44.4% p = 0.526 Days re-hospitalized NP 3.78 (8.8) Control 3.49 (6.5) p = 0.514 Physician office visits NP 9.94 (8.5) Control 11.72 (7.7) p = 0.036 Home health care days NP 4.99 (8.7) Control 5.57 (9.3) p = 0.485	adults, can reduce primary health care visits as per study
McClellan, 2012 [63] England To evaluate the clinical effectiveness of soft tissue injury	RS ^ Equivalence Trial: designed to show that two interventions do not differ in either direction by more than a pre-specified	372 patients with peripheral soft tissue injury, older than 16 years, were eligible for management by any of three professionals:	Diagnosis Prescribing Clinical Procedures Education	1) *Functional recovery to upper / lower extremity 2) **Preference-based health utility scores using the	1) *Functional recovery to upper / lower extremity at 8 weeks Percentage return to normal function; MCID (minimal clinically important difference) of 9 95% CIs Dr 45 to 80 (63.3%), (68/123) ESP 52.5 to 65.0 (59.2%), (72/126) ENP 55.0 to 66.3 (60.0%), (73/123)	Equivalence margin was set at five, calculated using the smallest minimal clinically important difference (MCID) from all outcome measures

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
management by emergency NPs and extended scope physiotherapists compared to routine care provided by doctors in an emergency department (ED) **Secondary Prevention** reducing risks / threats to health in a condition that has already occurred to halt or slow progress[13] **Post hoc analysis McClellan (2013)** *A randomised trial comparing the cost effectiveness of different emergency department healthcare professionals in soft tissue injury management* **Appendix I-5**	unimportant or insignificant amount, the equivalence margin (i.e. a two-sided statistical test)[85] Eight week study period *Acute Care Emergency Department* A single, inner city, adult ED of University Hospitals Bristol NHS Foundation Trust *Feb.17, 2017* £ 1.00 Great Britain = $1.62 Canadian £ 0.62 Great Britain = $1.00 Canadian	Emergency NPs (ENPs), Extended Scope Physiotherapists (ESPs), ED Doctor *Intervention* = patient management from arrival to discharge by ENP or ESP ENP (n = 123) ESP (n = 126) *Contro*l = routine ED Doctor care from arrival to discharge (n =123)		Short Form-6D (SF-6D) 3)**Medication administration 4) **Global quality of life (SF-36) 5) **Number of days unable to work	2) **Preference-based health utility scores at 8 weeks for percentage recovery; MCID of 5 95% CIs Dr 86.2-105.8 (92.2%) (68/123) ESP 93.2-100 (94.3%) (72/126) ENP 87.8 to 99.5 (92.2%) (73/123) 3) **Medication administration Dr 42.2% patients ESP 3.6% patients ENP 23.2% patients Differences between groups $p < 0.001$ 4) **Overall Quality of Life at 8 weeks 95% CIs to the Physical Component of SF-12v2 Dr −3.8-10.1 (3.2) on 68/123 patients ESP 0.2-4.6 (2.4) on 72/126 patients ENP 1.6-6.5 (4.1) on 73/123 patients 5) **Numbers of days off work at 8 weeks; MCID of 5 95% CIs Dr (0.0 days - 6.0 days) n=68 ESP (0.75 days - 2.0 days) n=72 ENP (1.0 days - 2.5 days) n=73	ENPs and ESPs were reported to be clinically equivalent to routine care provided by doctors as per study Main analysis was by intention-to-treat; a per-protocol analysis was also undertaken (McClellan, 2012, p.3), though no per-protocol data is shown

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
Johnson-Mallard, 2007 [70] U.S. To test the effects of an educational / behavioural intervention on knowledge and perceived risk of sexually transmitted infections (STIs) in women of childbearing age, presumably in good health at baseline **Primary Prevention:** preventing disease or injury before it ever occurs[13]	IPT ^^ Study duration two weeks *Primary Health Care* Set at two different American universities; study authors affiliated with the University of South Florida, Tampa, Florida	104 female college students, 18 - 48 years in presumably good health, and not yet exposed to lectures on sexually transmitted infections (STIs) *Intervention* = a brief, 30 minute educational / behavioral intervention delivered by an NP at one week (n =51) *Control* = no educational / behavioral intervention (n = 53)	<u>Only 1domain:</u> Education	1) Knowledge of sexually transmitted infections (STIs), including knowledge of pre and post-natal morbidity / mortality 2) Perceived risk of sexually transmitted infections (STIs)	*Endpoints not pre-specified as primary / secondary* 1) Mean (SD) STI knowledge two weeks following pre-test (higher scores indicate greater knowledge) one week post-intervention NP 26.1 (2.6) Control 21.0 (2.3) $p < 0.0001$ 2) Mean (SD) perceived risk of STI (lower scores indicate lower perceived risk) at 2 weeks NP 4.0 (1.0) Control 7.9 (2.3) $p < 0.0001$	Findings may assist NPs in reducing knowledge gaps related to STI morbidity associated with reproductive health: pelvic inflammatory disease, chronic pelvic pain, infertility, ectopic pregnancy, compromised birth outcomes (premature delivery, stillbirths, neonatal deaths, and infant disorders), and cervical cancer At the time of this trial, women were being diagnosed with two-thirds of the estimated annual 12 million new cases of STIs in the U.S.

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
Hannan, 2012 [69] U.S. To examine the effects of a low cost telephone intervention provided by a pediatric NP, for the first two months post-birth in low-income families of healthy, first time mothers who delivered a healthy, full-term single infant **Primary Prevention:** preventing disease or injury before it ever occurs[13]	RS ^ *Primary Health Care* Intervention occurred for first 2 months post-birth, delivered offsite via telephone. Study patients were recruited prior to discharge from Jackson Memorial Hospital, in the inner city of Miami, South Florida	139 healthy first-time mothers, 18 years or older, each of whom delivered a healthy, full-term single infant; low-income family *Intervention* = follow-up phone-calls by pediatric NP with 'back-up' pediatric physician available for consultation (n =70) *Control* = routine hospital discharge and a pediatrician appointment in 2 months (n =69)	Diagnosis Education Care Coordination NPs were Masters prepared pediatric NPs with a minimum of 10 years' experience; salary of $40.21/ hour, from Area Health Education Center (AHEC) data base	1) Maternal health: perceived stress, social support, physical health 2) Infant health: routine medical visits for immunizations, weight gain measurements 3) Infant morbidity: urgent care visits, Emergency Room (ER) visits, re-hospitalizations	*Endpoints not pre-specified as primary / secondary* 1) Maternal Health Outcomes at 2 months Post Birth • Mean (SD) Perceived Maternal Health NP 18.61 (1.74); Control 17.2 (2.69) p < 0.0004 • Mean (SD) Perceived Stress NP 14.71(3.95); Control 24.64(4.61) p < 0.0001 • Perception of Social Support Differences non-significant 2) Infant Health Outcomes at 2 months Post Birth • Infant vaccinations NP 92.8% (65/70); Control 84.1% (58/69) p = 0.186 • Weight Gain Differences non-significant 3) Infant Morbidity at 2 months Post Birth • Urgent-care-centre visits NP 3.6% (5/139); Control 2.2% (3/139) p = 0.48 • Emergency room visits NP 7.2% (10/139); Control 11.5% (16/139) p = 0.179 • Hospitalizations NP 0.7% (1/139); Control 2.2% (3/139) p = 0.30 4) Mean (SD) healthcare charges (not total costs) at 2 months	Attrition: 7/70 (10%) intervention mothers were unable to be contacted post-discharge due to dis-connected telephones As per study, follow-up phone calls by a pediatric NP to low-income first-time mothers in good health, with healthy full term infants, can be an effective, safe, and relatively low cost intervention that may improve maternal and infant health outcomes

Author, Year Country Purpose Level of Prevention	Design, Duration Setting	Patients (N)	NP Intervention Domains	Endpoints	Outcomes Outcome data analyzed by Intention to Treat, on the basis of all randomized patients, as randomized, unless otherwise noted	Comments
Feb. 17, 2017 $1.00 U.S = $1.31 Canadian $0.76 U.S. = $1.00 Canadian				4)Associated health care charges: urgent care visits, Emergency Room (ER) visits, re-hospitalizations, and NP phone service	• Urgent-Care-Centre NP $376 ($27) range $294-$482 Control $351($15) range $267–$402 p = 0.47 • Emergency Room NP $104 ($267) range $365-$1,080 Control $245 ($538) range $298–$2,410 p = 0.13 • Hospitalizations NP $51 ($423) range $3,547 (only 1 hospitalization); Control $764 ($3,847) range $9,153–$24,012 p = 0.29 • NP phone service Average total phone-calls $23.83 / mother Total NP group phone-calls $1,598.00 ($7.61) Control N/A Total Healthcare charges NP $14,333 Control $70,834 Difference $56, 501, p < 0.05	

*Primary Endpoint **Secondary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT)

17 Tertiary (3^0) Prevention[13] RCTs
Pioro (2001),[71] Allen (2002),[44] Jones (2002),[66] Ansari (2003),[45] Hill (2003),[55] Tranmer (2004),[46] Fairall (2005),[8] Goessens (2006), [47] Nathan (2006),[49] McCarrier (2009),[7] Mitchell (2009),[54] Ralston (2009),[6] Huizinga (2010),[51] Kim (2013),[53] Sawatsky (2013),[48] Berkhoff (2014),[50] Mertens (2014)[68]

10 Secondary (2^0) Prevention[13] RCTs
Ganz (2000),[61] Cooper (2002),[62] Williams (2005),[60] Krichbaum (2007),[64] Dierick-van Daele (2009),[67] ter Bogt (2009),[56] Schuttelaar (2010),[59] McCorkle (2009),[52] Enguidanos (2012),[65] McClellan (2012)[63]

2 Primary (1^0) Prevention[13] RCTs Johnson-Mallard (2007),[70] Hannan (2012)[69]

Appendix K Landmark RCTs Conducted upon the Formal Origin of the NP Role

Author, Year Country **Setting & Site** **Duration & Design**	**Intervention**	**Endpoint-Outcomes**		**Comments**
Spitzer[29] 1974 Burlington, Ontario, Canada *Primary Health Care* Single family practice clinic, not associated with university or hospital One year study from July 01, 1971-July 01, 1972 RS^ Cluster RCT Unit of random allocation = family Definition of 'family:' person or group sharing a common provincial health insurance number Non-Inferiority Trial: to assess the effects of NP care compared to GP care on patient outcomes in a single family practice clinic, with the non-inferiority margin set at 5%. Five% worse = greatest degree of worse functional outcomes tolerated from NP care before declared "inferior"[97]	*Intervention* = NP care; families equally divided between 2 NPs n = 540 families, including 1529/4325 patients *Control* = GP care; families equally divided between 2 GPs n = 1058 families, including 2796/4325 patients 2:1 Ratio of Random Allocation of 1598 families, since one half of the family physician case load was considered appropriate for newly trained NPs Study Practitioners **2** GPs with 9 & 14 years' experience **2** Nurses with 11 & 22 years' experience, *trained by an inter-professional 1 year, part-time program* (from colleges of Nursing & Medicine at McMaster University, prior to start of trial) *for the 'co-practitioner' role of NP*	I. Patient Health Status at 1 year 1. Physical status of NP patients was at best, the same or 1-2 % lower than that in GP patients 2. Emotional function was 0.4% lower in the NP group, & social function was 0.7% higher in the NP group, compared to the GP group II. Clinician Activities *Two methods to measure 'quality of care:'* 1. NP and GP management of 10 'indicator conditions'(select types of diseases, symptoms, states or injuries, not known to the GPs / NPs) *Percent of episodes rated as 'adequate management'* NP 69% of episodes GP 66% of episodes 2. Prescribing for 13 common drugs *Percent of prescriptions rated as 'adequate management'* NP 71% of prescriptions GP 75% of prescriptions III. Clinic Activities *Intervention effect on clinic profits:* 5% drop in gross revenue, related to no billing for NP services. The 22% increase in families served, would have created a 9% increase in income for the clinic had regulations permitted billing for NP services	Benefits experienced by new clinic families were not accompanied by a new model of care. Without changes made to address both types of clinicians' services, by regulatory bodies governing reimbursement for services, the positive gains experienced by new clinic families were not sustained over the long term. Non-Inferiority Trial One-sided analysis showed a probability of NPs' patients being 'worse off' by 5% or more,' equal to 0.008, or a likelihood of 1 chance out of 125 chances[97] At end of trial 22% net increase to *1952 clinic families, from original 1598 clinic families*	At one year follow-up, June 30, 1973 "New Plateau of Saturation" *2256 clinic families, a 41% net increase in families receiving care* Post-randomization consent (Zelen design) for family's clinical allocation, with option to decline Attrition 7 families refused their assignment: 2 from the GP group, 2 from the NP group; 3 families had a member under care by a GP for a long term condition *Drop-out rate* NP 0.9% GP 0.7% No individual data shown *Deaths* NP 4 GP 18

Author, Year Country Setting & Site Duration & Design	Intervention	Endpoint-Outcomes		Comments
Spitzer[96] 1973 southern Ontario, Canada *Primary Health Care* 14 private family practices not associated with university or hospital, located within 50 miles of Hamilton, excluding metropolitan Toronto Study period 12 months; April 1971 to March 1972 IPT^^ RCT Unit of random allocation = nurse Seven nurses were randomly assigned to receive NP training; the corresponding practices became intervention practices Purpose: to assess the effect of the one year, part-time education program from the Colleges of Nursing and Medicine, McMaster University, on the roles of primary care NPs and GPs	*Intervention* = care from 'GP + NP' n = 7 family practices; 7 RNs newly trained as NPs *Control* = usual care from 'GP + RN' n = 7 family practices Administration of questionnaires, time and motion studies, and observation of practices were undertaken by trained interviewers and observers from the Health Sciences Field Survey Unit of McMaster University Logistic difficulties prevented a true set of "before" measurements, prior to start date of the trial. Obtaining the "before" measurements would have required an unacceptable postponement of the NP educational program. Instead 'Time 1' values were measured in April & May 1971, as soon as possible after the onset of the trial; Time 2 was March 1972	<u>Research Questions</u> 1. What were the financial effects on practices, GPs and NPs? *Intervention Practices* Net earnings increased in 3 practices, remained unchanged in 2, and decreased in 1 practice, without reimbursement for unsupervised NP services[98] *Control Practices* Net earnings increased in 1 practice, remained unchanged in 4, and decreased in 1 practice[98] 2. a) What was the effect on job satisfaction for GPs, NPs and RNs? GPs' satisfaction scores at intervention practices were reported to be 71% satisfied and above, for all aspects measured. The largest reduction in satisfaction scores was measured regarding 'salary,' with a 25% difference between 96% of GPs at control practices to only 71% of GPs at intervention practices satisfied with salary. Except for 'relationship with colleagues,' all aspects of job satisfaction remained similar or improved for NPs compared to RNs. b) What was the effect on views of each professional role, reported *from the perspective of GPs*?	Clinical activities identified by GPs as "exclusively GP activities" were lowered at all time points in the intervention group; at end of trial, activities that were viewed as interchangeable increased in all categories c) How are activities of GPs & NPs altered? (i.e. change in the proportion of clinical & non-clinical activities) NPs spent ~ 50% more time in clinical work than RNs & ~ ½ the time in non-clinical work. GPs' time in clinical & non-clinical work, differed between groups by only 1-2%	<u>Attrition</u> 2 practices dropped-out before the end of the trial: 1 control practice became university-affiliated and 1 intervention practice experienced financial and professional dis-satisfaction. Clinical activity data presented in Figures 4 & 5 was only physician-reported without presentation of NP-reported data

*Primary Endpoint ^ Role Substitution (RS) ^^ Interprofessional Team (IPT)

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