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## The degree of integration of non-dispensing pharmacists in primary care practice and the impact on health outcomes: A systematic review

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### ABSTRACT

**Background:** A non-dispensing pharmacist conducts clinical pharmacy services aimed at optimizing patients individual pharmacotherapy. Embedding a non-dispensing pharmacist in primary care practice enables collaboration, probably enhancing patient care. The degree of integration of non-dispensing pharmacists into multidisciplinary health care teams varies strongly between settings. The degree of integration may be a determinant for its success.

**Objectives:** This study investigates how the degree of integration of a non-dispensing pharmacist impacts medication related health outcomes in primary care.

**Methods:** In this literature review we searched two electronic databases and the reference list of published literature reviews for studies about clinical pharmacy services performed by non-dispensing pharmacists physically co-located in primary care practice. We assessed the degree of integration via key dimensions of integration based on the conceptual framework of Walshe and Smith. We included English language studies of any design that had a control group or baseline comparison published from 1966 to June 2016. Descriptive statistics were used to correlate the degree of integration to health outcomes. The analysis was stratified for disease-specific and patient-centered clinical pharmacy services.

**Results:** Eighty-nine health outcomes in 60 comparative studies contributed to the analysis. The accumulated evidence from these studies shows no impact of the degree of integration of non-dispensing pharmacists on health outcomes. For disease specific clinical pharmacy services the percentage of improved health outcomes for none, partial and fully integrated NDPs is respectively 75%, 63% and 59%. For patient-centered clinical pharmacy services the percentage of improved health outcomes for none, partial and fully integrated NDPs is respectively 55%, 57% and 70%.

**Conclusions:** Full integration adds value to patient-centered clinical pharmacy services, but not to disease-specific clinical pharmacy services. To obtain maximum benefits of clinical pharmacy services for patients with multiple medications and comorbidities, full integration of non-dispensing pharmacists should be promoted.

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### 1. Introduction

The aging of the population results in increasingly complex medication-related needs.<sup>1</sup> To sustain the economic viability of health care the majority of elderly patients should be treated in primary care. To incorporate specific pharmaceutical expertise,

some primary care practices have embedded a non-dispensing pharmacist (NDP, also: clinical pharmacist or clinical pharmacy specialist).

NDPs in primary care practice conduct clinical pharmacy services (CPS) that primarily focus on chronic disease management. CPS are usually multifaceted, including medication therapy reviews, counselling and medication education. These services can be aimed at patients with a specific chronic condition such as diabetes, cardiovascular disease or COPD (“disease-specific CPS”), or at a more heterogeneous group of patients at risk of drug related problems, such as patients with multimorbidity and polypharmacy (“patient-centered CPS”). Disease-specific CPS focusses on evidence-based protocolled care, while patient-centered CPS entails a more non-standardized and holistic approach.<sup>2</sup>

Some NDPs are fully integrated into the health care team,<sup>3,4</sup> whereas others only temporarily provide a specific CPS.<sup>5</sup> Common opinion is that integrated care for patients with chronic conditions may improve patient outcomes.<sup>6–8</sup> CPS have been shown to positively affect surrogate outcomes, such as blood pressure, glycemic control and lipid goal attainment.<sup>9–13</sup> Evidence of the effect of CPS on clinical endpoints, such as mortality, hospitalizations and health related quality of life, is less clear probably due to very heterogeneously defined CPS as well as strongly differing study settings.<sup>12,14</sup>

Both aspects are features of the degree of integration of the NDP who delivers the CPS. The degree of integration of NDPs into the health care team may be a determinant for its success, but this association has never been properly assessed. Therefore, we conducted a systematic review to investigate how the degree of integration of an NDP impacts health outcomes in primary care.

## 2. Methods

The protocol of this systematic review has been published in the PROSPERO register. The registration number is: CRD42016017506.<sup>15</sup>

### 2.1. Search strategy

We searched PubMed and Embase from 1966 to June 2016. A trained librarian, in consultation with researchers, developed a search strategy (Appendix Table 1). Also, we manually searched the reference list of systematic reviews and background articles about clinical pharmacy interventions in primary care for additional citations.

Potentially relevant studies were identified by two reviewers (AH and LB) based on predetermined inclusion criteria in a two-step procedure: 1) title and abstract, 2) screening of the full text. In case disagreement about inclusion could not be resolved by discussion between the two reviewers, a third reviewer (AB or MB) was consulted to reach consensus. We used the PRISMA checklist to conduct and report the systematic literature review.<sup>16</sup>

### 2.2. Study selection

Both USA and non-USA comparative studies of any design that had a control group or baseline comparison were included if they met the following criteria:

### 2.3. The intervention

1. comprised at least one key component of a chronic disease management service aimed at individual ambulatory patients;
2. was conducted by an NDP who had a regular and ongoing relationship with the primary care practice and was at least

part-time physically present and at that time not involved in work related to community pharmacy;

3. measured a relevant clinical or patient reported health outcome or a proxy of a relevant health outcome (e.g. improvement of medication errors).

Studies were excluded if the intervention was delivered in a specialty or off-site clinic without collaboration with the general practitioner (GP), or if it was a pilot of an already included study or a secondary analysis. Also, unpublished studies and studies published in languages other than English were not taken into account for analysis.

### 2.4. Dependant variable: degree of integration

Our main focus was the degree of integration of NDPs, which we assessed via key dimensions of integration from the conceptual framework of Walshe and Smith<sup>17</sup>: organizational, informational, clinical, functional, financial and normative integration (Table 1). The financial integration could not be taken into account as most interventions were project funded studies. The key dimensions were scored dichotomous (yes/no). A positive score on zero to two dimensions of integration was defined as “no integration”. A positive score on three or four dimensions of integration was defined as “partial integration” and a positive score on all five dimensions was defined as “full integration”. Prescriptive authority was taken into account to assess clinical integration, see Table 3.

### 2.5. Primary outcome: health outcomes

The primary outcomes of the intervention were either real clinical health outcomes, such as mortality, or surrogate clinical health outcomes, such as HbA1c, lipids and blood pressure. In addition to clinical health outcomes, we included patient reported health outcomes, such as health related quality of life and proxies of health outcomes, such as quality of care performance indicators.

### 2.6. Data collection process

Other extracted data included the duration of the intervention, study size, primary outcomes, specification of the CPS (disease-specific or patient-centered) and the number of involved practices and NDPs. The primary outcomes of the intervention were categorized as either “positive”, “negative” or “no effect”. A positive outcome was defined as a statistically significant difference ( $p$  value  $< 0.05$ ) compared to the control group or baseline. A negative outcome being the opposite and no effect as no statistically significant difference between intervention and control group or baseline.

Two authors independently extracted the data and one author cross-checked all extracted data. Differences were resolved in discussion. In case of dissensus, a third researcher was consulted. If we were unable to score the dimensions of integration – despite contacting the corresponding author for additional information and verifying complementary study protocols – the study was excluded for synthesis.

### 2.7. Quality assessment

We used the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool to assess: selection bias, study design, confounders, data collection methods, withdrawals and drop-outs. Given the nature of the included studies, blinding of the participants and outcome assessors was generally not possible. Therefore, this criterion was not included in the quality

**Table 1**Key dimensions of integrated care for chronic disease management,<sup>17</sup> tailored to the setting of a non-dispensing pharmacist in primary care practice.

|                 |  |
|-----------------|--|
| Organizational: | Organizational design and governance arrangements<br><i>Measurable element:</i> an umbrella organization or network, or NDP has permanent position within primary care practice  |
| Informational:  | Shared access of clinical information systems<br><i>Measurable element:</i> GP and NDP work with integrated clinical information systems   |
| Clinical:       | Delivery of rational and continuous clinical care to patients<br><i>Measurable elements:</i> multiprofessional teams, NDP performs patient counselling and follow-up, face-to-face communication between GP and NDP, patient directed activities outside the scope of the intervention, prescribing authority of the NDP |
| Functional:     | Supportive administrative and functional elements<br><i>Measurable element:</i> shared education or administrative support by primary care practice staff  |
| Financial:      | Financial arrangements and payment system<br><i>Measurable element:</i> n/a  |
| Normative:      | Shared vision, goals and values<br><i>Measurable element:</i> collaboratively designed protocols with shared goals and visions of the pharmaceutical intervention  |

assessment. Two authors independently assessed each study and resolved disagreement by consensus or by consulting a third reviewer.

### 2.8. Data synthesis

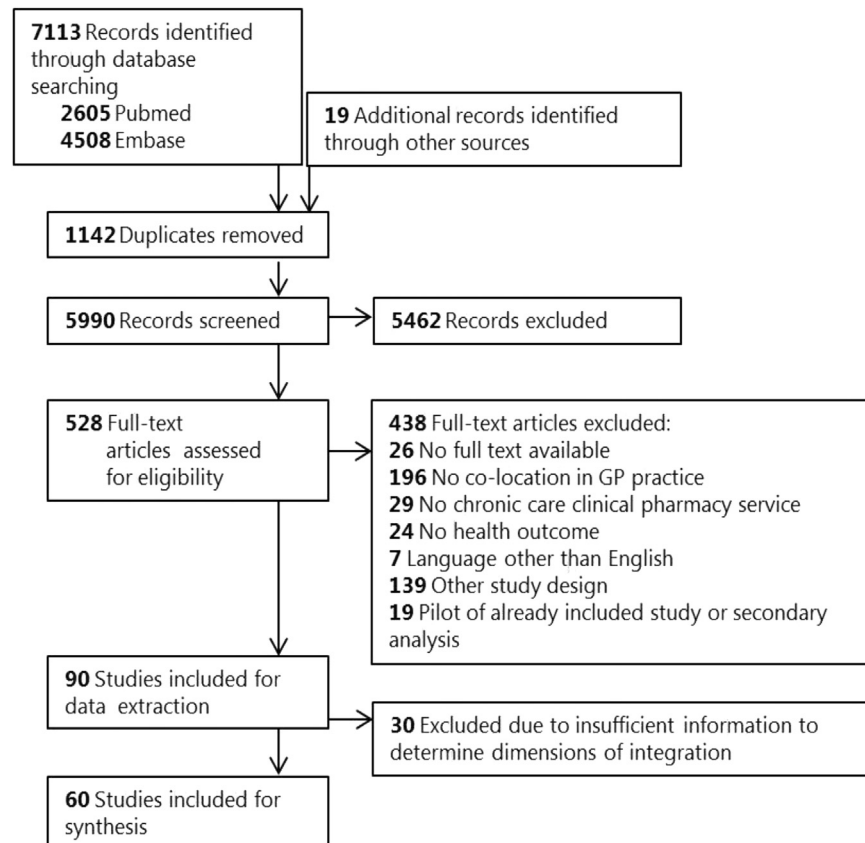
The included studies were heterogeneous regarding the type of CPS, enrolled participants, number of practices, involved NDPs and measured health outcomes. Therefore, it was inappropriate to perform statistical aggregation of findings. To investigate how the degree of integration of an NDP impacts health outcomes we plotted the number of improved primary outcomes against the total number of assessed primary outcomes. We stratified the analysis for disease-specific CPS and patient-centered CPS.

### 3. Results

Ninety studies were included for data extraction (Fig. 1). For thirty studies we were unable to determine the degree of integration of the NDP and were excluded (Appendix Table 2a/b). We grouped studies by type of CPS: disease-specific CPS (n = 43) and patient-centered CPS (n = 17).

#### 3.1. Summary of included studies

The included studies consisted of 35 RCTs, 12 two group cohort studies and 13 one group cohort studies. The median of the study population was 140 patients (interquartile range 76–321). The duration of the interventions ranged from 1 to 60 months. The median of the number of involved practices and NDPs was 1



**Fig. 1.** Flowchart of the study selection.

(interquartile range 1–6) and 2 (interquartile range 1–4), respectively. The majority of the studies were performed in the United States of America (USA) ( $n = 43$ ) (Tables 2a and 2b).

### 3.2. Methodological quality

The methodological quality was high in 18 studies (30%), moderate in 34 studies (57%) and low in 8 studies (13%). 35 studies (58%) had a strong design, with described randomization processes. Eight studies (13%) had a high participation rate and were very likely to be representative to the target population. Forty studies (67%) controlled for at least 80% of relevant confounders and 48 studies (80%) used valid and reliable data collection tools. 29 studies (48%) had a follow-up rate of at least 80% (Table 3).

### 3.3. Synthesis of results

We assessed 89 health outcomes in 60 comparative studies: 54 clinical health outcomes (mainly surrogate health outcomes such as blood pressure or HbA1c), 12 patient reported health outcomes, such as health related quality of life and 23 proxies of health outcomes, such as medication errors (see Table 4). CPS conducted by NDPs showed a significant positive effect on 62% (55/89) of assessed health outcomes. The other 34 health outcomes showed no statistically significant difference compared to control group or baseline. None of the included studies measured a negative impact on health outcomes. The effect of CPS on surrogate clinical health outcomes and proxies of health outcomes was high: 67% (36/54) and 78% (18/23) of these outcomes improved. Patient reported health outcomes were less frequently reported ( $n = 12$ ) and showed improvement in one trial.

We related the dimensions of integration to the degree of integration. We found 14 studies (23%) in which the NDPs were not or minimally integrated into the health care team (positive score on 0–2 dimensions of integration). 71% ( $n = 10$ ) of NDPs had shared access to patient medical records (informational integration). Yet, integration on all other dimensions was low: organizational 14% ( $n = 2$ ), normative 14% ( $n = 2$ ), functional 7% ( $n = 1$ ) and clinical 7% ( $n = 1$ ).

We identified 19 studies (32%) in which the NDPs were partially integrated (positive score on 3–4 dimensions of integration). All but one (95%) had shared access to patient medical records. Integration on the clinical, functional and normative dimension was 68% ( $n = 13$ ) and 47% ( $n = 9$ ) of NDPs were permanently employed within the practice or worked within an umbrella organization or network (organizational integration).

We found 27 studies (45%) in which the NDPs were fully integrated within the primary care practice (positive score on 5 dimensions of integration). This involved permanent employment within the organization, or an umbrella organization or network, shared information systems, shared education or administrative support and a profound clinical role with shared goals and visions, such as a collaborative practice agreement to enhance cooperation in the delivery of CPS.

For each level of integration (none-partial-full), we plotted the number of improved primary outcomes against the total number of assessed primary outcomes (Fig. 2). The accumulated evidence from these studies suggests that there is no impact of the degree of integration of NDPs on health outcomes. The percentage of improved health outcomes for none, partial and fully integrated NDPs is respectively 63% (based on 19 assessed health outcomes within 14 different studies), 61% (based on 23 assessed health outcomes within 19 different studies) and 62% (based on 47

assessed health outcomes within 27 different studies). Also, after stratifying the health outcomes into clinical, patient reported and proxies of health outcomes, no association can be identified between the degree of integration of NDPs and an improvement on health outcomes.

### 3.4. Stratification of the results according to type of CPS

We included 43 studies about disease-specific CPS, in which 61 health outcomes, mainly surrogate clinical health outcomes ( $n = 51$ ) were assessed, of which 67% showed a significant positive effect. Five patient reported health outcomes and five proxies of health outcomes were reported, of which 20% ( $n = 1$ ) and 60% ( $n = 3$ ) showed improvement, respectively. Within this subgroup of CPS services, we found 8 studies (19%) in which the NDPs were not or minimally integrated into the health care team, 14 studies (33%) in which the NDPs were partially integrated and 21 studies (49%) in which the NDPs were fully integrated within the primary care team. For disease-specific CPS the percentage of improved health outcomes in studies with not, partial and fully integrated NDPs is respectively 75%, 63% and 59%. Our data suggest a negative association between integration and improvement on health outcomes for disease-specific CPS (Fig. 2).

We included 17 studies about patient-centered CPS and assessed 28 health outcomes, mainly proxies of health outcomes ( $n = 18$ ) of which 83% showed a significant positive effect. In total, 7 patient reported health outcomes were reported of which none showed improvement. A small number of surrogate clinical health outcomes was reported ( $n = 3$ ) and 2 were positively affected by the NDP provided services. We found 6 studies (35%) in which the NDPs were not or minimally integrated into the health care team, 5 studies (29%) in which the NDPs were partially integrated and 6 studies (35%) in which the NDPs were fully integrated within the primary care team. For patient-centered CPS the percentage of improved health outcomes in studies with not, partial and fully integrated NDPs is respectively 55%, 57% and 70%. Therefore, our data suggest a positive association between integration and improvement on health outcomes for patient-centered CPS (Fig. 2).

## 4. Discussion

We evaluated the impact of the degree of integration of NDPs on health outcomes in primary care. Although we found that the degree of integration of NDPs did not impact health outcomes in the overall group, subgroup analysis suggests that full integration of an NDP may be especially relevant for patient-centered CPS.

An explanation of why full integration of an NDP is more relevant for patient-centered interventions than disease-specific interventions is provided by Weick.<sup>76</sup> Integration enables NDPs to manage interruptions in the care trajectory of an individual patient. Being in close relation with both GPs and patients, NDPs can pick up the small clues that signal lapses in the care trajectory. The degree of integration showed a trend towards a negative association with the health outcomes of disease-specific CPS. The diseases-specific CPS included in this study were based upon a set protocol. These standardized care trajectories are less prone to errors and allowing for variety may not have an added value. Reliability – defined as compliance to the protocols – seems to be more effective.<sup>77</sup>

Almost all studies reported surrogate health outcomes rather than clinical endpoints such as hospitalization or mortality. Disease-specific CPS mainly described surrogate clinical health outcomes (e.g. HbA1c, lipids and blood pressure), while patient-centered CPS

**Table 2a**

Study characteristics of disease-specific clinical pharmacy services (n = 43).

| Author (year)                        | Country   | No. intervention practices/No. NDPs | Duration intervention (months) | No. patients in intervention group | Dimension of integration |               |                       |            |           | Primary outcomes (effect)   |
|--------------------------------------|-----------|-------------------------------------|--------------------------------|------------------------------------|--------------------------|---------------|-----------------------|------------|-----------|---|
|                                      |           |                                     |                                |                                    | Organizational           | Informational | Clinical <sup>a</sup> | Functional | Normative |   |
| <b>Diabetes (n=16)</b>               |           |                                     |                                |                                    |                          |               |                       |            |           |   |
| Choe (2005) <sup>18</sup>            | USA       | 1/1                                 | 24                             | 41                                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | HbA1C (+)   |
| Coast-Senior (1998) <sup>19</sup>    | USA       | 2/4                                 | 3–11                           | 23                                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | Glycemic control (+)  |
| Heisler (2012) <sup>4</sup>          | UK        | 5/11                                | 14                             | 1797                               | Yes                      | Yes           | Yes                   | Yes        | Yes       | BP (0)  |
| Henry (2013) <sup>20</sup>           | USA       | 1/2                                 | 3                              | 93                                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | Guideline adherence (0), HbA1C (+)  |
| Ip (2013) <sup>21</sup>              | USA       | 1/1                                 | 12                             | 147                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | HbA1c, LDL-C and BP (+) and goal attainment (+), 10-year CVRR (+)                               |
| Irons (2002) <sup>22</sup>           | USA       | 1/2                                 | 32                             | 87                                 | Yes                      | No            | Yes                   | No         | Yes       | Glycemic control (0)  |
| Jameson (2010) <sup>23</sup>         | USA       | 13/1                                | 12                             | 52                                 | No                       | Yes           | No                    | Yes        | Yes       | HbA1c (0)   |
| McAdam-Marx (2015) <sup>24</sup>     | USA       | 10/3                                | 48                             | 303                                | Yes                      | Yes           | Yes                   | No         | Yes       | Glycemic control (+)  |
| McCord (2006) <sup>25</sup>          | USA       | 1/1                                 | 4                              | 316                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | HbA1c (+), BP (0), lipids (+)   |
| McFarland (2012) <sup>26</sup>       | USA       | 4/3                                 | 6                              | 36                                 | Yes                      | No            | Yes                   | Yes        | Yes       | HbA1c (0)   |
| Mourão (2012) <sup>27</sup>          | Brazil    | 6/2                                 | 6                              | 50                                 | No                       | No            | No                    | No         | No        | HbA1c (0)   |
| Rothman (2005) <sup>28</sup>         | USA       | 1/3                                 | 12                             | 112                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | HbA1c (+), LDL-C (0), BP (+)  |
| Salvo (2012) <sup>29</sup>           | USA       | 1/1                                 | 18                             | 69                                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | HbA1c (+)   |
| Scott (2006) <sup>30</sup>           | USA       | 1/1                                 | 9                              | 76                                 | No                       | Yes           | Yes                   | Yes        | Yes       | HbA1c (+)   |
| Shane-McWorther (2005) <sup>31</sup> | USA       | 1/1                                 | 36                             | 176                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | HbA1c (0), lipids (0), BP (0)   |
| Simpson (2011) <sup>32</sup>         | Canada    | 5/2                                 | 12                             | 131                                | Yes                      | Yes           | Yes                   | Yes        | No        | BP (+)  |
| <b>Hypertension (n=11)</b>           |           |                                     |                                |                                    |                          |               |                       |            |           |   |
| Bex (2011) <sup>33</sup>             | USA       | 4/6                                 | 18                             | 573                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | BP (+)  |
| Bogden (1998) <sup>34</sup>          | USA       | 1/1                                 | 6                              | 49                                 | No                       | Yes           | No                    | No         | No        | BP (+)  |
| Borenstein (2003) <sup>35</sup>      | USA       | 1/1                                 | 12                             | 98                                 | No                       | Yes           | No                    | Yes        | Yes       | BP (+)  |
| Carter (2008) <sup>36</sup>          | USA       | 5/2                                 | 9                              | 101                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | BP (+)  |
| Hirsch (2014) <sup>37</sup>          | USA       | 1/2                                 | 9                              | 166                                | No                       | Yes           | Yes                   | Yes        | Yes       | BP (+)  |
| Hunt (2008) <sup>38</sup>            | USA       | 9/5                                 | 12                             | 230                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | BP (+)  |
| Magid (2013) <sup>39</sup>           | USA       | 10/≥10                              | 6                              | 175                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | BP (+)  |
| Margolis (2013) <sup>40</sup>        | USA       | 16/8                                | 18                             | 228                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | BP (+)  |
| Mehos (2000) <sup>41</sup>           | USA       | 1/1                                 | 6                              | 18                                 | No                       | No            | No                    | No         | No        | BP (+)  |
| O'Neill (2014) <sup>42</sup>         | USA       | 1/1                                 | 1                              | 63                                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | BP (+)  |
| Wong (2013) <sup>43</sup>            | Hong Kong | 1/?                                 | 6                              | 92                                 | No                       | No            | No                    | No         | No        | BP (0)  |
| <b>Dyslipidaemia (n=5)</b>           |           |                                     |                                |                                    |                          |               |                       |            |           |   |
| Billups (2005) <sup>44</sup>         | USA       | 16/16–48                            | 12                             | 5550                               | Yes                      | Yes           | No                    | No         | Yes       | LDL-C (+)   |
| Bogden (1997) <sup>5</sup>           | USA       | 1/1                                 | 6                              | 47                                 | No                       | Yes           | No                    | No         | No        | LDL-C (+)   |
| Smith (2013) <sup>45</sup>           | USA       | 2/1                                 | ?                              | 213                                | Yes                      | Yes           | Yes                   | Yes        | Yes       | Lipid profile   |
| Straka (2005) <sup>46</sup>          | USA       | 2/2                                 | 6                              | 359                                | No                       | Yes           | Yes                   | No         | Yes       | LDL-C (+)   |
| Tahaine (2011) <sup>47</sup>         | Jordan    | 1/1                                 | 6                              | 73                                 | No                       | No            | No                    | No         | Yes       | LDL-C (+)   |
| <b>Metabolic syndrome (n=1)</b>      |           |                                     |                                |                                    |                          |               |                       |            |           |   |
| Hammad (2011) <sup>48</sup>          | Jordan    | 6/2                                 | 6                              | 112                                | Yes                      | Yes           | No                    | No         | No        | Metabolic syndrome status (+)   |
| <b>Heart failure (n=1)</b>           |           |                                     |                                |                                    |                          |               |                       |            |           |   |
| Lowrie (2012) <sup>49</sup>          | UK        | 174/27                              | 60                             | 1090                               | No                       | Yes           | Yes                   | No         | No        | Composite of death or hospital admission for worsening heart failure (0)                        |
| <b>Depression (n=3)</b>              |           |                                     |                                |                                    |                          |               |                       |            |           |   |
| Adler (2004) <sup>50</sup>           | USA       | 9/5                                 | 6                              | 268                                | No                       | Yes           | Yes                   | Yes        | No        | Antidepressant use rate (+), depression severity (0)  |
| Capoccia (2004) <sup>51</sup>        | USA       | 1/2                                 | 12                             | 41                                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | Depression symptoms (0)   |
| Finley (2003) <sup>52</sup>          | USA       | 1/?                                 | 6                              | 75                                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | Adherence to antidepressant (+), patient satisfaction (+), clinical and functional severity (0) |

(continued on next page)

Table 2a (continued)

| Author (year)  | Country | No. intervention practices/No. NDPs | Duration intervention (months) | No. patients in intervention group | Dimension of integration |               |                       |            |           | Primary outcomes (effect)  |
|--|---------|-------------------------------------|--------------------------------|------------------------------------|--------------------------|---------------|-----------------------|------------|-----------|--|
|  |         |                                     |                                |                                    | Organizational           | Informational | Clinical <sup>a</sup> | Functional | Normative |  |
| <b>Osteoporosis (n=1)</b>                                    |         |                                     |                                |                                    |                          |               |                       |            |           |  |
| Hall (2009) <sup>53</sup>                                    | USA     | 1/4                                 | ?                              | 22                                 | Yes                      | Yes           | Yes                   | No         | Yes       | Compliance with treatment guidelines (+)   |
| <b>Cardiovascular disease (n=1)</b>                          |         |                                     |                                |                                    |                          |               |                       |            |           |  |
| Evans (2010) <sup>54</sup>                                   | Canada  | 1/1                                 | 6                              | 176                                | No                       | Yes           | Yes                   | No         | Yes       | 10 year cardiovascular risk reduction (0)  |
| <b>Diabetes + hypertension (n=2)</b>                         |         |                                     |                                |                                    |                          |               |                       |            |           |  |
| Edelman (2010) <sup>55</sup>                                 | USA     | 2/2                                 | 12                             | 133                                | Yes                      | Yes           | Yes                   | Yes        | No        | BP (+), HbA1c (0)  |
| Neto (2011) <sup>56</sup>                                    | Brazil  | 1/4                                 | 36                             | 97                                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | 10 year cardiovascular risk reduction (+)  |
| <b>Diabetes and/or dyslipidaemia (n=1)</b>                   |         |                                     |                                |                                    |                          |               |                       |            |           |  |
| Hetro (2015) <sup>57</sup>                                   | USA     | 1/?                                 | 6                              | 61                                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | HbA1c (+), LDL-C (0), BMI (0)  |
| <b>Diabetes, hypertension, dyslipidaemia or asthma (n=1)</b> |         |                                     |                                |                                    |                          |               |                       |            |           |  |
| Koenigsfeld (2012) <sup>58</sup>                             | USA     | 3/3                                 | 13                             | 131 + 427+299 + 27                 | Yes                      | Yes           | Yes                   | Yes        | Yes       | Achieving goal levels for DM (0), hypertension (+) and % on asthma controller medication (0) |

(+) = positive effect, (0) = no effect, BP = Blood Pressure, CVRR = Cardiovascular Risk Reduction, HbA1c = glycosylated haemoglobin, LDL-C = low-density lipoprotein cholesterol.

<sup>a</sup> See Appendix Table 3 for specification.

Table 2b

Study characteristics of patient-centered clinical pharmacy services (n = 17).

| Author (year)                  | Country   | No. practices/No. NDPs | Duration intervention (months) | Study size intervention group (patients) | Dimension of integration |               |                       |            |           | Primary outcome(s) (effect)   |
|--------------------------------|-----------|------------------------|--------------------------------|--|--------------------------|---------------|-----------------------|------------|-----------|---|
|                                |           |                        |                                |  | Organizational           | Informational | Clinical <sup>a</sup> | Functional | Normative |   |
| Avery (2012) <sup>59</sup>     | UK        | 72/?                   | 12                             | 3812                                     | No                       | Yes           | No                    | No         | No        | Three prescribing appropriateness indicators (+)                          |
| Berdine (2012) <sup>60</sup>   | USA       | 1/1                    | 36                             | 200                                      | Yes                      | Yes           | Yes                   | Yes        | Yes       | Lipids (+), A1c (0) and BMI (+)   |
| Carter (2001) <sup>61</sup>    | USA       | 9/51?                  | 12                             | 523                                      | Yes                      | Yes           | Yes                   | Yes        | No        | Patient satisfaction (0), HRQoL (0)                                       |
| Davis (2007) <sup>62</sup>     | USA       | 6/12                   | 5                              | 79                                       | Yes                      | Yes           | No                    | Yes        | No        | MAI (+)   |
| Freeman (2013) <sup>63</sup>   | Australia | 1/1                    | 0–12                           | 314                                      | Yes                      | Yes           | Yes                   | Yes        | Yes       | Uptake of recommendations from medication review (+)                      |
| Galt (1998) <sup>64</sup>      | USA       | 1/1                    | 12                             | 336                                      | Yes                      | Yes           | Yes                   | Yes        | Yes       | Reduction in use of unessential medications (+)                           |
| Hanlon (1996) <sup>65</sup>    | USA       | 1/1                    | 12                             | 105                                      | No                       | Yes           | No                    | No         | No        | MAI (+), HRQoL (0), ADE (0)   |
| Hogg (2009) <sup>66</sup>      | Canada    | 1/1                    | 12–18                          | 121                                      | Yes                      | Yes           | Yes                   | Yes        | Yes       | QoC for CDM (+)   |
| Isetts (2006) <sup>67</sup>    | USA       | 6/7                    | 12                             | 285                                      | Yes                      | Yes           | Yes                   | Yes        | Yes       | Patients' perceptions of care (0), HRQoL (0)                              |
| Isetts (2008) <sup>68</sup>    | USA       | 6/7                    | 12                             | 256                                      | Yes                      | Yes           | Yes                   | Yes        | Yes       | Quality-of-care performance measures for hypertension and cholesterol (+) |
| Krska (2001) <sup>69</sup>     | UK        | ?/?                    | 3                              | 168                                      | No                       | Yes           | No                    | Yes        | No        | Resolved PCI (+), HRQoL (0)   |
| Lenander (2014) <sup>70</sup>  | Sweden    | 1/1                    | 12                             | 107                                      | No                       | Yes           | No                    | Yes        | Yes       | Resolved MRPs (0), No. of medications (+)                                 |
| Pindolia (2009) <sup>71</sup>  | USA       | 1/7                    | 24                             | 520                                      | Yes                      | Yes           | No                    | No         | No        | Improvement on clinical outcome rules (0)                                 |
| Roth (2013) <sup>72</sup>      | USA       | ½                      | 6                              | 64                                       | No                       | Yes           | No                    | No         | Yes       | Resolved MRPs (+)   |
| Sellers (2003) <sup>73</sup>   | Canada    | 24/12                  | 5                              | 431                                      | No                       | Yes           | No                    | No         | No        | No. of daily doses (0)  |
| Tan (2014) <sup>74</sup>       | Australia | 2/2                    | 6                              | 82                                       | No                       | Yes           | Yes                   | Yes        | No        | Resolved MRPs (+)   |
| Zermansky (2001) <sup>75</sup> | UK        | 4/1                    | 12                             | 581                                      | No                       | Yes           | No                    | Yes        | Yes       | No. of changes to repeat prescription changes (+)                         |

(+) = positive effect, (0) = no effect, ADE = Adverse Drug Events, BMI = Body Mass Index, BP = Blood pressure, CDM = Chronic Disease Management, HbA1c = glycosylated haemoglobin, HRQoL = Health Related Quality of Life, LDL-C = low-density lipoprotein cholesterol, MAI = Medication Appropriateness Index, MRP = Medication Related Problem, PCI = Pharmaceutical Care Issues, QoC = Quality of Care.

<sup>a</sup> See Appendix Table 3 for specification.

**Table 3**  
Quality assessment of included studies.

| Author (year)                        | Selection bias | Study design | Confounders | Data collection | Drop-outs | Global   |
|--------------------------------------|----------------|--------------|-------------|-----------------|-----------|----------|
| Adler (2004) <sup>50</sup>           | Weak           | Strong       | Strong      | Strong          | Strong    | Moderate |
| Avery (2012) <sup>59</sup>           | Weak           | Strong       | Weak        | Strong          | Strong    | Weak     |
| Berdine (2012) <sup>60</sup>         | Moderate       | Moderate     | Weak        | Strong          | Weak      | Weak     |
| Bex (2011) <sup>33</sup>             | Moderate       | Moderate     | Weak        | Strong          | Moderate  | Moderate |
| Billups (2005) <sup>44</sup>         | Moderate       | Moderate     | Weak        | Strong          | Strong    | Moderate |
| Bogden (1997) <sup>5</sup>           | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| Bogden (1998) <sup>34</sup>          | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| Borenstein (2003) <sup>35</sup>      | Weak           | Strong       | Moderate    | Strong          | Strong    | Moderate |
| Capoccia (2004) <sup>51</sup>        | Moderate       | Strong       | Strong      | Moderate        | Strong    | Strong   |
| Carter (2001) <sup>61</sup>          | Moderate       | Strong       | Weak        | Strong          | Weak      | Weak     |
| Carter (2008) <sup>36</sup>          | Weak           | Strong       | Strong      | Strong          | Moderate  | Moderate |
| Choe (2005) <sup>18</sup>            | Strong         | Strong       | Strong      | Moderate        | Moderate  | Strong   |
| Coast-Senior (1998) <sup>19</sup>    | Moderate       | Weak         | Weak        | Moderate        | Strong    | Weak     |
| Davis (2007) <sup>62</sup>           | Strong         | Moderate     | Weak        | Strong          | Moderate  | Moderate |
| Edelman (2010) <sup>55</sup>         | Weak           | Strong       | Strong      | Strong          | Strong    | Moderate |
| Evans (2010) <sup>54</sup>           | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| Finley (2003) <sup>52</sup>          | Moderate       | Strong       | Strong      | Strong          | Weak      | Moderate |
| Freeman (2013) <sup>63</sup>         | Strong         | Moderate     | Weak        | Moderate        | Moderate  | Moderate |
| Galt (1998) <sup>64</sup>            | Weak           | Moderate     | Weak        | Moderate        | Weak      | Weak     |
| Hall (2009) <sup>53</sup>            | Moderate       | Moderate     | Strong      | Strong          | Weak      | Moderate |
| Hammad (2011) <sup>48</sup>          | Strong         | Strong       | Strong      | Strong          | Strong    | Strong   |
| Hanlon (1996) <sup>65</sup>          | Strong         | Strong       | Strong      | Moderate        | Strong    | Strong   |
| Heisler (2012) <sup>4</sup>          | Moderate       | Strong       | Strong      | Strong          | Weak      | Moderate |
| Henry (2013) <sup>20</sup>           | Moderate       | Moderate     | Weak        | Weak            | Moderate  | Weak     |
| Hetro (2015) <sup>57</sup>           | Moderate       | Moderate     | Weak        | Strong          | Moderate  | Moderate |
| Hirsch (2014) <sup>37</sup>          | Weak           | Strong       | Strong      | Strong          | Strong    | Moderate |
| Hogg (2009) <sup>66</sup>            | Moderate       | Strong       | Strong      | Moderate        | Strong    | Strong   |
| Hunt (2008) <sup>38</sup>            | Weak           | Strong       | Strong      | Strong          | Weak      | Weak     |
| Ip (2013) <sup>21</sup>              | Moderate       | Moderate     | Strong      | Strong          | Moderate  | Moderate |
| Irons (2002) <sup>22</sup>           | Moderate       | Moderate     | Strong      | Strong          | Moderate  | Moderate |
| Isetts (2006) <sup>67</sup>          | Weak           | Moderate     | Moderate    | Strong          | Moderate  | Moderate |
| Isetts (2008) <sup>68</sup>          | Moderate       | Moderate     | Strong      | Strong          | Weak      | Moderate |
| Jameson (2010) <sup>23</sup>         | Weak           | Strong       | Strong      | Strong          | Strong    | Moderate |
| Koenigsfeld (2012) <sup>58</sup>     | Moderate       | Moderate     | Weak        | Strong          | Moderate  | Moderate |
| Krska (2001) <sup>69</sup>           | Moderate       | Strong       | Strong      | Moderate        | Strong    | Strong   |
| Lenander (2014) <sup>70</sup>        | Moderate       | Strong       | Strong      | Weak            | Moderate  | Moderate |
| Lowrie (2012) <sup>49</sup>          | Weak           | Strong       | Strong      | Strong          | Strong    | Moderate |
| Magid (2013) <sup>39</sup>           | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| Margolis (2013) <sup>40</sup>        | Moderate       | Strong       | Weak        | Strong          | Strong    | Moderate |
| McAdam-Marx (2015) <sup>24</sup>     | Moderate       | Moderate     | Strong      | Strong          | Moderate  | Moderate |
| McCord (2006) <sup>25</sup>          | Moderate       | Moderate     | Weak        | Strong          | Moderate  | Moderate |
| McFarland (2012) <sup>26</sup>       | Moderate       | Moderate     | Strong      | Strong          | Moderate  | Moderate |
| Mehos (2000) <sup>41</sup>           | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| Mourão (2012) <sup>27</sup>          | Strong         | Strong       | Strong      | Strong          | Moderate  | Strong   |
| Neto (2011) <sup>56</sup>            | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| O'Neill (2014) <sup>42</sup>         | Moderate       | Weak         | Strong      | Strong          | Moderate  | Moderate |
| Pindolia (2009) <sup>71</sup>        | Weak           | Moderate     | Weak        | Strong          | Moderate  | Weak     |
| Roth (2013) <sup>72</sup>            | Moderate       | Moderate     | Strong      | Strong          | Strong    | Moderate |
| Rothman (2005) <sup>28</sup>         | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| Salvo (2012) <sup>29</sup>           | Moderate       | Moderate     | Weak        | Strong          | Moderate  | Moderate |
| Scott (2006) <sup>30</sup>           | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| Sellers (2003) <sup>73</sup>         | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| Shane-McWorther (2005) <sup>31</sup> | Moderate       | Moderate     | Weak        | Strong          | Moderate  | Moderate |
| Simpson (2011) <sup>32</sup>         | Weak           | Strong       | Strong      | Strong          | Strong    | Moderate |
| Smith (2013) <sup>45</sup>           | Moderate       | Moderate     | Strong      | Strong          | Moderate  | Moderate |
| Straka (2005) <sup>46</sup>          | Strong         | Strong       | Strong      | Strong          | Strong    | Strong   |
| Tahaineh (2011) <sup>47</sup>        | Strong         | Strong       | Weak        | Strong          | Moderate  | Moderate |
| Tan (2014) <sup>74</sup>             | Moderate       | Moderate     | Strong      | Moderate        | Moderate  | Moderate |
| Wong (2013) <sup>43</sup>            | Moderate       | Strong       | Strong      | Strong          | Strong    | Strong   |
| Zermansky (2001) <sup>75</sup>       | Weak           | Strong       | Strong      | Moderate        | Strong    | Moderate |
| <b>Sum weak</b>                      | 14 (23%)       | 2 (3%)       | 18 (30%)    | 2 (3%)          | 8 (13%)   | 8 (13%)  |
| <b>Sum moderate</b>                  | 38 (63%)       | 23 (38%)     | 2 (3%)      | 10 (17%)        | 23 (38%)  | 34 (57%) |
| <b>Sum strong</b>                    | 8 (13%)        | 35 (58%)     | 40 (67%)    | 48 (80%)        | 29 (48%)  | 18 (30%) |

often used process outcomes (e.g. quality of care performance indicators) to measure the effect of the intervention. Also, we found a low impact of CPS on health related quality of life.<sup>51,61,65,67,69</sup> The effects of a multifaceted quality improvement service often do not extend as far as to health related quality of life.<sup>78</sup>

Fully integrated NDPs are permanently employed or work

within a network or umbrella organization (organizational integration), they usually have shared access to clinical information systems (informational integration), work in multiprofessional teams with face-to-face collaboration with the GP (clinical integration), have shared education and/or support staff for administrative functions (functional integration) and share a vision on

**Table 4**  
The impact of the degree on integration of NDPs on health outcomes in primary care.

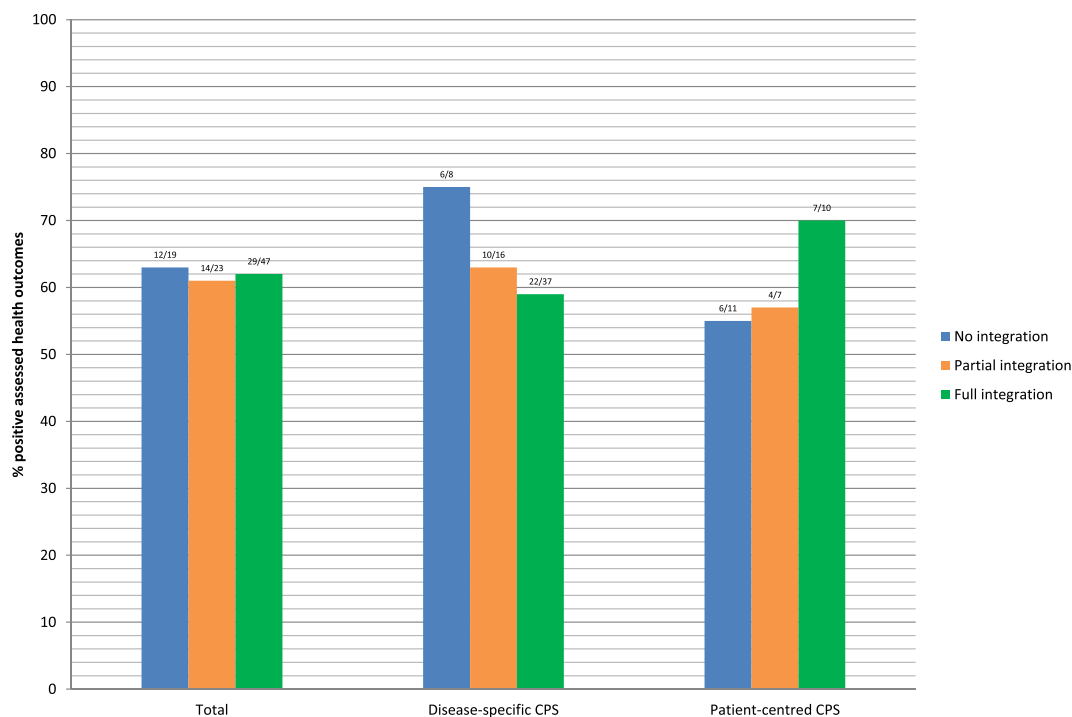
|  | All outcomes (n = 89) |                     |                    | Disease-specific CPS (no. of assessed outcomes: 61) |                     |                    | Patient-centered CPS (no. of assessed outcomes: 28) |                     |                   |
|--|-----------------------|---------------------|--------------------|---|---------------------|--------------------|---|---------------------|-------------------|
|  | No integration        | Partial integration | Full Integration   | No integration                                      | Partial integration | Full integration   | No integration                                      | Partial integration | Full integration  |
| <b>Clinical health outcomes</b>  |                       |                     |                    |   |                     |                    |   |                     |                   |
| Death or hospitalization   | 0/1 (1090)            |                     |                    | 0/1 (1090)  |                     |                    |   |                     |                   |
| <b>Surrogate clinical health outcomes</b>                                  |                       |                     |                    |   |                     |                    |   |                     |                   |
| HbA1c  | 1/1 (50)              | 2/6 (687)           | 8/11 (1369)        | 1/1 (50)  | 2/6 (687)           | 8/10 (1169)        |   |                     | 0/1 (200)         |
| Lipids   | 2/2 (120)             | 2/2 (5909)          | 4/7 (1225)         | 2/2 (120)   | 2/2 (5909)          | 3/6 (1025)         |   |                     | 1/1 (200)         |
| BP   | 2/3 (159)             | 4/4 (430)           | 7/11 (4198)        | 2/3 (159)   | 4/4 (430)           | 7/11 (4198)        |   |                     |                   |
| BMI  |                       |                     | 1/2 (261)          |   |                     | 0/1 (61)           |   |                     | 1/1 (200)         |
| Metabolic syndrome status  | 1/1 (112)             |                     |                    | 1/1 (112)   |                     |                    |   |                     |                   |
| Cardiovascular risk reduction  |                       | 0/1 (176)           | 2/2 (244)          |   | 0/1 (176)           | 2/2 (244)          |   |                     |                   |
| Subtotal   | 6/8 (75%)             | 8/13 (62%)          | 22/33 (68%)        | 6/8 (75%)   | 8/13 (62%)          | 20/30 (67%)        |   |                     | 2/3 (67%)         |
| <b>Patient reported health outcomes</b>                                    |                       |                     |                    |   |                     |                    |   |                     |                   |
| HRQoL  | 0/2 (273)             | 0/1 (523)           | 0/2 (453)          |   |                     | 0/1 (168)          | 0/2 (273)   | 0/1 (523)           | 0/1 (285)         |
| Patient satisfaction, perceptions of care                                  | 0/1 (105)             | 0/1 (523)           | 1/2 (360)          |   |                     | 1/1 (75)           | 0/1 (105)   | 0/1 (523)           | 0/1 (285)         |
| Depression severity  |                       | 0/1 (268)           | 0/2 (116)          |   | 0/1 (268)           | 0/2 (116)          |   |                     |                   |
| Subtotal   | 0/3 (0%)              | 0/3 (0%)            | 1/6 (17%)          |   | 0/1 (0%)            | 1/4 (25%)          | 0/3 (0%)  | 0/2 (0%)            | 0/2 (0%)          |
| <b>Proxies of health outcomes</b>  |                       |                     |                    |   |                     |                    |   |                     |                   |
| Adherence rate   |                       | 1/1 (268)           | 1/1 (75)           |   | 1/1 (268)           | 1/1 (75)           |   |                     |                   |
| Reduction of (unwanted) medications  | 0/1 (431)             | 2/2 (688)           | 1/1 (336)          |   |                     |                    | 0/1 (431)   | 2/2 (688)           | 1/1 (336)         |
| Medication errors, pharmaceutical care issues, prescribing appropriateness | 6/7 (12.293)          | 3/4 (290)           | 3/5 (753)          |   | 1/1 (22)            | 0/2 (120)          | 6/7 (12.293)  | 2/3 (268)           | 3/3 (633)         |
| Uptake of recommendations from MR  |                       |                     | 1/1 (314)          |   |                     |                    |   |                     | 1/1 (314)         |
| Subtotal   | 6/8 (67%)             | 6/7 (86%)           | 6/8 (75%)          |   | 2/2 (100%)          | 1/3 (33%)          | 6/8 (75%)   | 4/5 (80%)           | 5/5 (100%)        |
| <b>Total</b>   | <b>12/19 (63%)</b>    | <b>14/23 (61%)</b>  | <b>29/47 (62%)</b> | <b>6/8 (75%)</b>                                    | <b>10/16 (63%)</b>  | <b>22/37 (59%)</b> | <b>6/11 (55%)</b>                                   | <b>4/7 (57%)</b>    | <b>7/10 (70%)</b> |

No. of improved outcomes/no. of assessed outcomes (no. of intervention patients).

For each health outcome, the number of studies that demonstrated significant improvement is divided by the total number of assessed studies. Since studies can include more than one primary outcome, the total number of assessed outcomes (89) exceeds the total number of included studies (60).

The numbers in parentheses reflect the accumulated number of intervention patients in studies assessing the specific health outcome.

BP = Blood pressure, BMI = Body Mass Index, HbA1c = glycosylated haemoglobin, HRQoL = Health Related Quality of Life, MR = Medication Review.



**Fig. 2.** Outcomes by degree of integration of NDPs on health outcomes in primary care. For each category of integration the total number of significant improved outcomes is divided by the total number of assessed outcomes. The results are also stratified by disease-specific CPS and patient-centered CPS.



patient care with clinicians (normative integration). Clinical integration into a multidisciplinary primary care team provides greater opportunities for both formal and informal communication, probably enhancing patient care.<sup>63</sup> Also, expanding the clinical role of the NDP by allocating prescribing privileges might be beneficial.<sup>79</sup> Within disease-specific CPS, more than half of the NDPs were authorized to make medication changes within a defined scope of practice. Within patient-centered CPS, only 2 studies showed NDPs with prescribing authority. In these kind of services, with a more holistic approach to pharmaceutical care, prescribing authority would entail the whole spectrum of medications. The current absence of prescribing authority might have restricted the impact of the CPS on health outcomes.

CPS performed in isolation may negatively influence the quality of care.<sup>80</sup> There is one systematic review that described the effectiveness of NDPs co-located in primary care practice.<sup>9</sup> The importance of follow-up and face-to-face communication with the patient's GP (clinical integration) is highlighted. Other available studies described the effectiveness of CPS in different outpatient settings.<sup>10–14</sup> This study is the first to unravel the association between the extent of NDP integration in clinical care and drug related health outcomes.

#### 4.1. Limitations

This review has a number of limitations. Similar to most literature reviews, there might have been publication bias. Also, CPS can like all cognitive interventions be subject to the Hawthorne-effect. The Hawthorne-effect might, at least partly, explain the absence of any negative health outcome in the included studies. The interventions and outcomes assessed in this review were heterogeneous. Also, we were unable to assess the impact of health care systems on the degree of integration of NDPs and on the success of the provided services. Moreover, the study population, duration of the intervention, number of practices and involved NDPs differed widely, limiting our options to assess the independent effect of integration and to pool data. The problem of heterogeneity in

clinical pharmacy intervention studies has been previously addressed.<sup>9,12,14,81–83</sup> Hence, we cannot draw too strong conclusions about the impact of integration – as reflected by the wording we choose. Lastly, the positive association we found between the degree of integration and the effect of patient-centered CPS was based upon a limited number of studies (n = 17). Random effects cannot be ruled out. Additional research is required when new studies about integrated clinical pharmacy services in primary care become available.

#### 4.2. Implications

This study has several implications for practitioners and policy-makers. Integration on *all* dimensions for *all* types of chronic disease management services performed by NDPs in primary care practice may not be necessary. Integration on *all* dimensions should be promoted for individually tailored, i.e. patient-centered CPS.

#### 5. Conclusion

To obtain maximum benefits of CPS for patients with multiple medications and comorbidities, full integration of NDPs should be stimulated.

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#### Appendix A

**Table 1**

Search strategies for Pubmed and Embase

| Pubmed search June 2016  | Embase search June 2016  |
|--|--|
| ("pharmacist"[Title/Abstract] OR "pharmacists"[Title/Abstract] OR "pharmaceutical service"[Title/Abstract] OR "pharmaceutical services"[Title/Abstract] OR "pharmacy"[Title/Abstract] OR "pharmacists"[MeSH Terms] OR "pharmaceutical services"[MeSH Terms])   | pharmacist:ti,ab OR pharmacists:ti,ab OR pharmacy:ti,ab OR 'pharmaceutical service':ti,ab OR 'pharmaceutical services':ti,ab OR 'pharmacist'/exp OR 'pharmacy'/exp   |
| ("family practice"[Title/Abstract] OR "general practitioner"[Title/Abstract] OR "primary care"[Title/Abstract] OR "general practitioners"[Title/Abstract] OR "general practice"[Title/Abstract] OR "family physician"[Title/Abstract] OR "physicians, family"[MeSH Terms] OR "family practice"[MeSH Terms] OR "general practitioners"[MeSH Terms] OR "general practice"[MeSH Terms])   | 'family practice':ti,ab OR 'general practitioner':ti,ab OR 'general practitioners':ti,ab OR 'general practice':ti,ab OR 'community dwelling':ti,ab OR 'family physician':ti,ab OR 'community dwelling':ti,ab OR 'ambulatory patient':ti,ab OR 'ambulatory elderly':ti,ab OR 'ambulatory patients':ti,ab OR 'primary care':ti,ab OR 'general practice'/exp OR 'general practitioner'/exp  |
| ("patient care"[Title/Abstract] OR "interprofessional relation"[Title/Abstract] OR "interprofessional relations"[Title/Abstract] OR "cooperation"[Title/Abstract] OR "collaboration"[Title/Abstract] OR "consultation"[Title/Abstract] OR "referral"[Title/Abstract] OR "refer"[Title/Abstract] OR "home medicines review"[Title/Abstract] OR "medication review"[Title/Abstract] OR "medication reviews"[Title/Abstract] OR "community dwelling"[Title/Abstract] OR "ambulatory patient"[Title/Abstract] OR "ambulatory elderly"[Title/Abstract] OR "ambulatory patients"[Title/Abstract] OR "pharmaceutical care"[Title/Abstract] OR "drug utilization review"[Title/Abstract] OR patient care[MeSH Terms] OR interprofessional relations[MeSH Terms] OR cooperative behaviour [MeSH Terms] OR counselling[MeSH Terms] OR professional role [MeSH Terms] OR (referral and consultation[MeSH Terms] OR "drug utilization review"[MeSH Terms] OR "review"[Title/Abstract]) | 'patient care':ti,ab OR 'interprofessional relation':ti,ab OR 'interprofessional relations':ti,ab OR cooperation:ti,ab OR collaboration:ti,ab OR consultation:ti,ab OR referral:ti,ab OR refer:ti,ab OR 'home medicines review':ti,ab OR 'medication review':ti,ab OR 'medication reviews':ti,ab OR review:ti,ab OR 'pharmaceutical care':ti,ab OR 'drug utilization review':ti,ab OR 'patient care'/exp OR 'patient referral'/exp |

**Table 2a**  
excluded studies with disease-specific CPS

| Author (year)                        | Dimension of integration |               |          |            |           |
|--------------------------------------|--------------------------|---------------|----------|------------|-----------|
|                                      | Organizational           | Informational | Clinical | Functional | Normative |
| Anaya (2008) <sup>84</sup>           | No                       | Yes           | Yes      | N/A        | Yes       |
| Barnes (2014) <sup>85</sup>          | Yes                      | Yes           | No       | N/A        | N/A       |
| Bruhn (2013) <sup>86</sup>           | Yes                      | Yes           | Yes      | N/A        | N/A       |
| Carter (2015) <sup>87</sup>          | Yes                      | Yes           | Yes      | No         | N/A       |
| Chung (2014) <sup>88</sup>           | Yes                      | Yes           | N/A      | N/A        | Yes       |
| Cording (2002) <sup>89</sup>         | Yes                      | Yes           | N/A      | Yes        | Yes       |
| Duran-Parrondo (2011) <sup>90</sup>  | No                       | N/A           | Yes      | N/A        | Yes       |
| Erickson (1997) <sup>91</sup>        | Yes                      | Yes           | No       | N/A        | No        |
| Gums (2014) <sup>92</sup>            | Yes                      | Yes           | Yes      | No         | N/A       |
| Gums (2015) <sup>93</sup>            | Yes                      | Yes           | Yes      | No         | N/A       |
| Jacobs (2012) <sup>94</sup>          | No                       | Yes           | No       | N/A        | No        |
| Jamieson (2010) <sup>95</sup>        | No                       | Yes           | N/A      | N/A        | N/A       |
| Johnson (2010) <sup>96</sup>         | No                       | N/A           | N/A      | N/A        | N/A       |
| Kelly Hester (2000) <sup>97</sup>    | No                       | N/A           | N/A      | No         | No        |
| Monte (2009) <sup>98</sup>           | No                       | N/A           | No       | Yes        | N/A       |
| Shane-McWorther (2015) <sup>99</sup> | N/A                      | No            | N/A      | No         | Yes       |
| Solomon (1998) <sup>100</sup>        | Yes                      | N/A           | No       | N/A        | N/A       |
| Stading (2009) <sup>101</sup>        | Yes                      | Yes           | N/A      | N/A        | N/A       |
| Thumar (2014) <sup>102</sup>         | No                       | Yes           | No       | Yes        | N/A       |
| Tobari (2010) <sup>103</sup>         | Yes                      | Yes           | No       | N/A        | N/A       |
| Trompeter (2009) <sup>104</sup>      | No                       | Yes           | N/A      | Yes        | N/A       |
| Villa (2009) <sup>105</sup>          | N/A                      | N/A           | N/A      | N/A        | N/A       |

**Table 2b**  
excluded studies with patient-centered CPS

| Author (year)                  | Dimension of integration |               |          |            |           |
|--------------------------------|--------------------------|---------------|----------|------------|-----------|
|                                | Organizational           | Informational | Clinical | Functional | Normative |
| Hamley (1997) <sup>106</sup>   | Yes                      | N/A           | N/A      | N/A        | N/A       |
| Harris (2009) <sup>107</sup>   | Yes                      | Yes           | No       | N/A        | N/A       |
| Jameson (1995) <sup>108</sup>  | N/A                      | N/A           | No       | N/A        | N/A       |
| Jameson (2001) <sup>109</sup>  | N/A                      | Yes           | No       | N/A        | N/A       |
| Laucka (1996) <sup>110</sup>   | No                       | Yes           | No       | N/A        | N/A       |
| Lowe (2000) <sup>111</sup>     | No                       | No            | No       | N/A        | N/A       |
| Morrison (2015) <sup>112</sup> | No                       | Yes           | No       | N/A        | Yes       |
| Taylor (2003) <sup>113</sup>   | No                       | Yes           | No       | N/A        | N/A       |

**Table 3**  
Clinical integration based upon six measurable elements. The NDP was considered clinical integrated when the result on  $\geq$  four elements was positive ("Yes").

| Ref.                              | Patient counselling by NDP | Follow-up by NDP | Face-to-face communication GP and NDP | Multiprofessional collaboration ( $\geq 3$ care providers) | Other patient directed activities outside scope of intervention | Prescribing authority |
|-----------------------------------|----------------------------|------------------|---------------------------------------|--|---|-----------------------|
| Adler (2004) <sup>50</sup>        | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |
| Avery (2012) <sup>59</sup>        | No                         | Yes              | Yes                                   | No   | No  | No                    |
| Berdine (2012) <sup>60</sup>      | Yes                        | Yes              | Yes                                   | No   | Yes   | Yes                   |
| Bex (2011) <sup>33</sup>          | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |
| Billups (2005) <sup>44</sup>      | No                         | Yes              | No                                    | No   | Yes   | No                    |
| Bogden (1997) <sup>5</sup>        | Yes                        | No               | No                                    | No   | No  | No                    |
| Bogden (1998) <sup>34</sup>       | Yes                        | No               | Yes                                   | No   | No  | No                    |
| Borenstein (2003) <sup>35</sup>   | Yes                        | Yes              | No                                    | No   | No  | No                    |
| Capoccia (2004) <sup>51</sup>     | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| Carter (2001) <sup>61</sup>       | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| Carter (2008) <sup>36</sup>       | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |
| Choe (2005) <sup>18</sup>         | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |
| Coast-Senior (1998) <sup>19</sup> | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| Davis (2007) <sup>62</sup>        | Yes                        | Yes              | No                                    | No   | Yes   | No                    |
| Edelman (2010) <sup>55</sup>      | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |
| Evans (2010) <sup>54</sup>        | Yes                        | Yes              | Yes                                   | No   | Yes   | No                    |
| Finley (2003) <sup>52</sup>       | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| Freeman (2013) <sup>63</sup>      | Yes                        | No               | Yes                                   | Yes  | Yes   | No                    |
| Galt (1998) <sup>64</sup>         | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |
| Hall (2009) <sup>53</sup>         | Yes                        | Yes              | No                                    | Yes  | No  | Yes                   |
| Hammad (2011) <sup>48</sup>       | Yes                        | Yes              | Yes                                   | No   | No  | No                    |
| Hanlon (1996) <sup>65</sup>       | Yes                        | No               | Yes                                   | No   | No  | No                    |
| Heisler (2012) <sup>4</sup>       | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| Henry (2013) <sup>20</sup>        | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |

Table 3 (continued)

| Ref.                                 | Patient counselling by NDP | Follow-up by NDP | Face-to-face communication GP and NDP | Multiprofessional collaboration ( $\geq 3$ care providers) | Other patient directed activities outside scope of intervention | Prescribing authority |
|--------------------------------------|----------------------------|------------------|---------------------------------------|--|---|-----------------------|
| Hetro (2015) <sup>57</sup>           | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| Hirsch (2014) <sup>37</sup>          | Yes                        | Yes              | Yes                                   | No   | No  | Yes                   |
| Hogg (2009) <sup>66</sup>            | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |
| Hunt (2008) <sup>38</sup>            | Yes                        | Yes              | Yes                                   | No   | No  | Yes                   |
| Ip (2013) <sup>21</sup>              | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| Irons (2002) <sup>22</sup>           | Yes                        | Yes              | No                                    | No   | Yes   | Yes                   |
| Isetts (2006) <sup>67</sup>          | Yes                        | Yes              | Yes                                   | Yes  | No  | No                    |
| Isetts (2008) <sup>68</sup>          | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |
| Jameson (2010) <sup>23</sup>         | Yes                        | Yes              | Yes                                   | No   | No  | No                    |
| Koenigsfeld (2012) <sup>58</sup>     | Yes                        | Yes              | Yes                                   | No   | Yes   | No                    |
| Krska (2001) <sup>69</sup>           | Yes                        | Yes              | No                                    | Yes  | No  | No                    |
| Lenander (2014) <sup>70</sup>        | Yes                        | No               | Yes                                   | Yes  | No  | No                    |
| Lowrie (2012) <sup>49</sup>          | Yes                        | Yes              | Yes                                   | Yes  | No  | Yes                   |
| Magid (2013) <sup>39</sup>           | Yes                        | Yes              | No                                    | Yes  | Yes   | Yes                   |
| Margolis (2013) <sup>40</sup>        | Yes                        | Yes              | No                                    | Yes  | Yes   | Yes                   |
| McAdam-Marx (2015) <sup>24</sup>     | Yes                        | Yes              | Yes                                   | Yes  | No  | Yes                   |
| McCord (2006) <sup>25</sup>          | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| McFarland (2012) <sup>26</sup>       | No                         | Yes              | No                                    | Yes  | No  | Yes                   |
| Mehos (2000) <sup>41</sup>           | Yes                        | Yes              | No                                    | No   | No  | No                    |
| Mourão (2012) <sup>27</sup>          | Yes                        | Yes              | No                                    | No   | No  | Yes                   |
| Neto (2011) <sup>56</sup>            | Yes                        | Yes              | Yes                                   | Yes  | Yes   | No                    |
| O'Neill (2014) <sup>42</sup>         | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| Pindolia (2009) <sup>71</sup>        | Yes                        | Yes              | Yes                                   | No   | No  | No                    |
| Roth (2013) <sup>72</sup>            | Yes                        | Yes              | Yes                                   | No   | No  | No                    |
| Rothman (2005) <sup>28</sup>         | Yes                        | Yes              | Yes                                   | Yes  | No  | Yes                   |
| Salvo (2012) <sup>29</sup>           | Yes                        | Yes              | No                                    | Yes  | Yes   | Yes                   |
| Scott (2006) <sup>30</sup>           | Yes                        | Yes              | No                                    | Yes  | No  | Yes                   |
| Sellors (2003) <sup>73</sup>         | Yes                        | Yes              | Yes                                   | No   | No  | No                    |
| Shane-McWorther (2005) <sup>31</sup> | Yes                        | Yes              | No                                    | Yes  | Yes   | No                    |
| Simpson (2011) <sup>32</sup>         | Yes                        | Yes              | Yes                                   | Yes  | No  | No                    |
| Smith (2013) <sup>45</sup>           | Yes                        | Yes              | Yes                                   | Yes  | Yes   | Yes                   |
| Straka (2005) <sup>46</sup>          | Yes                        | Yes              | Yes                                   | No   | No  | Yes                   |
| Tahaine (2011) <sup>47</sup>         | Yes                        | Yes              | No                                    | No   | Yes   | No                    |
| Tan (2014) <sup>74</sup>             | Yes                        | No               | Yes                                   | Yes  | Yes   | No                    |
| Wong (2013) <sup>43</sup>            | Yes                        | No               | No                                    | No   | No  | No                    |
| Zermansky (2001) <sup>75</sup>       | Yes                        | Yes              | Yes                                   | No   | No  | No                    |

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