Appendix 7. Detailed description and discussion of the results based on outcomes, i.e. clinical, economic and humanistic.

The most important outcomes of this study are the clinical (mortality, morbidity), economic (health care utilities, health care costs) and humanistic (patient satisfaction, quality of life), and if they can be explained by improved adherence due to the interventions. As with the results of adherence, there was variation in how the results were presented between the studies. Some were only reported as statistically significant or not, either in words or statistical measures for interpretation, and some were only reported as effect sizes from which the statistically significance had to be interpreted.

Reminder interventions, DOT, web-based programmes and interventions performed by physicians, failed to show statistically improvements in outcomes. Simplified dosing, patient education, counselling with and without pharmacists prescribing showed mixed effects among the outcomes. Even if some of the studies reported absence the evidence of effect, they should not be interpreted as evidence to no effect, as more studies or different study types might be necessary to reveal an effect(112).

There was evidence that patient education had a positive effect on morbidity and patient satisfaction. Counselling had a positive effect on mortality and health care utilizations. Morbidity was also reduced when pharmacists prescribed medication. Since most of these improvements were based on the results of only one RCT, the evidence is weak.

Mortality

Of all the 9 RCTs that measured mortality, only one study reported a statistically significant effect on mortality.

Nieuwlaat, Wilczynski et al. 2014(13) reported mortality as outcome in Holland 2007(71), Chung 2011(68), Nazareth 2001(74) and Wu 2006(81). The result on mortality was missing in Holland 2007. For Chung 2011 and Nazareth 2001, quantitative data was not reported, nevertheless the systematic review reported the results as not significant, for alarm devices and pharmacist intervention, respectively. There was reported a statistically significant result on both adherence and mortality in Wu 2006, where the risk of all-cause mortality was reduced from 18 % to 11 % with the increased pharmacist intervention.

In Ngwatu, Nsengiyumva et al. 2018(63), the mortality result in the study Liu 2015(65), was mixed with data of treatment failure and loss to follow up.

Mathes, Antoine et al. 2014(59) reported results on mortality in Lester 2010(60), Mbuagbaw 2012(61) and Sarna 2008(62). In Lester 2010, adherence was improved, and mortality was 2 % lower in the nurse provided-SMS group compared to the control group. In contrast, mortality was 1.9 % higher for the patients receiving SMS and 2.7 % higher for the patients receiving nurse provided DOT compared to patients receiving usual care in Mbuagbaw 2012 and Sarna 2008, respectively. Both results were not statistically significant. In Sarna 2008 the adherence improved only during the intervention period.

The intervention period in these studies lasted from 12 weeks to 2 years. Naturally there would be a higher amount of deaths with a longer study period.

Several other studies have reported mortality outcomes in relation to adherence. A meta-analysis of 21 observational studies including 46 847 participants), showed that good adherence was associated with lower mortality. Both when the participant received placebo or beneficial drug therapy, the group with the good adherence reported 3.8 % less deaths than the poor adherence group. Since it was reported less deaths when the patients were on placebo instead of an active drug, the study concluded that the observed association between good adherence to placebo and mortality supports the "healthy adherer" effect, meaning that the patients took better care of their health (e.g. through diet, physical exercise, regular follow up with health care etc.). These actions by themselves can lower the risk of mortality. So, good adherence to drug therapy can be a surrogate marker for overall healthy behaviour among patients(34).

In Simpson et al 2006(34), good adherence was also associated with increased mortality for those patients who were on harmful drug therapy. This was also shown in a population-based observational study amongst 31 455 elderly patients who had survived acute myocardial infarction (AMI). The patients that had high and intermediate adherence to calcium channel blockers had a higher death rate than the patients who had a low adherence. At all, calcium channel blockers were considered to be a control in the study because of absence of clinical trial-proven survival benefits. In the same study some of the patients were given statins, and it improved survival of the patients with 4 % for the intermediate adherent and 8 % for the high adherent patients compared to the low adherent patients. For patients receiving β-blockers there was a similar but less pronounced association between adherence and mortality(33). This study shows the importance of evidence-based medicine. When the adherence was high for the unsuited medication, mortality increased, and when the adherence was high for the evidence-based medication, mortality decreased, favouring the suggestion that positive outcomes are caused by the drug's biological responsiveness (drug

effect)(33). In other words, improving adherence should not only be about the patient following the prescription. The prescription also must be the right choice for the patient's condition.

Morbidity

17 studies reported morbidity as outcome, with only 5 studies having statistically significant results on morbidity.

Bediang 2014(64), Liu 2015(65) and Mohammed 2016(66) were reported in Ngwatu, Nsengiyumva et al. 2018 (63), and adherence measures were missing. There was reported no difference between groups on mortality in Mohammed 2016. In Bediang 2014, the cure rate was 2 % higher in the SMS reminder group and the result was not statistically significant. In Liu 2015, the data on morbidity was not separated from mortality and loss to follow up.

In Mathes, Antoine et al. 2014 (59), it was reported 2.6 % more opportunistic infections in the SMS group than in the control group in Mbuagbaw 2012(61), however the results were not statistically significant on neither morbidity or adherence to antiretroviral therapy for HIV-infected patients. In Nieuwlaat, Wilczynski et al. 2014 (13) it was reported that simplified dosage regimen showed no statistically significant effect on adherence in Dejesus 2009(69), anyhow the patients reported a statistically significant effect on HIV symptoms, but the effect size was not reported.

As described in Normansell, Kew et al. 2017(82), pharmacist education in Mehuys 2008(83) lead to a statistically significant improved adherence, and exacerbations and asthma control were slightly improved, though not statistically significant. In the same systematic review, the study NCT00414817(84-86) was reported with no statistically significant effects on asthma control. Nieuwlaat, Wilczynski et al. 2014(13) reported that nurse-provided education and self-management had a positive effect on the patient self-reported asthma morbidity in Levy 2000, but qualitative data were missing.

Nieuwlaat, Wilczynski et al. 2014(13) also reported morbidity results in Murray 2007(73), Sadik 2005(77), Nieuwkerk 2012 (75), Pyne 2011 (76), Udelson 2009(79) and Vergouven 2005(80). Quantitative data were missing on the education intervention results on morbidity in Murray 2007 and Sadik 2005, but there was reported a positive effect both on adherence and heart failure symptoms. In Nieuwkerk 2012, adherence was improved with extended nurse care, but there was no effect on the patients' anxiety. In Pyne 2011, the patients experienced no effect on the severity of their depression, but they reported more depression free days, even the intervention did not show any effect on adherence. One can ask if the intervention itself, where the patients were more

exposed to care providers, might have increased their depression free days. In Udelson 2009 the intervention had no statistically significant effect on adherence or depressive symptoms, anyway the description of the intervention included carvedilol which is not an antidepressant agent. Antidepressant agents were used in Vergouven 2005, but the intervention did not lead to any statically significant improvement on adherence or depression.

In Bruhn 2013(88) described in Weeks, George et al 2016(37), the patients reported full adherence at the baseline, so it's unclear if the intervention had any effect in keeping up the patients' persistence as further data on adherence was not reported. Anyway, both the intervention groups had a statistically significant improvement in their grade of chronic pain, reporting 47.7 % and 38.6 % improvement.

Nurse provided education resulted in a slightly statistically significant improvement in adherence in Dash 2015(57), as cited in Al-aqeel, Gershuni et al. 2017(56). The improvement in morbidity was approximately 50 % higher in the intervention group compared to the control group, also being statistically significant.

In Pladevall 2015(93) cited in Zaugg, Korb-Savoldelli et al. 2018(92), the results of the physicians' management of their patients' adherence showed no statistically significant difference between groups. At 18 and 24 months the number of major atherosclerosis disease events was higher in the control group than in the intervention group, but at 36 months there was a higher number of incidents in the intervention group, however the results were not statically significant.

Dose and time between doses are key determinants of the magnitude and time-course of drug action. Non-adherence affects the concentration of the drug in the body. The action of the drug gradually fades during long intervals between doses. When a scheduled dose is omitted, the drug concentration in plasma declines, and can reach to zero if the next dose is delayed long enough(113). Consequently, in the studies where the medication relieves symptoms of conditions, patients will experience increased symptoms when they are not being adherent. In the RCTs measuring morbidity, only 4 studies reported both improved adherence and improved morbidity.

Non-adherent patients who experience less therapeutic effect, might be set on a higher dosage by clinicians, wrongly based on an assumption by the clinician that these patients are adherent. It can also lead to discontinuation on the assumption that the medicine is ineffective(114). This underlines the importance of revealing the patients' adherence before adjustments are made to the dose or by switching to another medication.

Health care utilizations

18 studies measured the effect on health care utilizations, 5 of them showed a statistically significant improvement.

The studies extracted from Weeks, George et al. (37), Margolis 2013(91), Hunt 2008(89) and Magid 2013(90) all contained pharmacist interventions with prescribing. Information about the effect and statistically significands in Margolis 2013 and Hunt 2008 was missing in the systematic reveiw. However, it was reported that the total number clinic visits (pharmacist + physician) was higher in the intervention group, simultaneous as the number of physician visits were lower in Hunt 2008. It was reported an effect on emergency department visits and hospitalizations that was close to zero Magid 2013, and the result was not significant.

Nieuwlaat, Wilczynski et al. 2014(13) reported no positive statistically significant results on health care utilization in Gould 2009(70), Holland 2007(71), Nazareth 2001(74), Sherrard 2009(78) and Udelson 2009(79). In the same systematic review it was reported that in Levy 2000(72) nurse provided education had positive effect on the patients' use of medical services, and in Wu 2006(81) pharmacist intervention showed a positive effect on ER visits and hospitalization, both studies had statistically significant results, also on adherence.

Normansell, Kew et al. 2017(82) reported results of interventions targeting asthma patients, Mehuys 2008(83), Price 2010(87) and NCT00414817(84-86) were extracted from that systematic review. In Mehuys 2008, the intervention group had a lower number of unscheduled visits to the health care provider and the result was not statistically significant. Price 2010 had an effect on unscheduled visits that was close to no difference at the same time as the confidence intervals showed both an important benefit and an important harm. The effect, benefit or harm, was not statistically significant. NCT00414817 showed no statistically significant effects.

In Williams 2010(94) and Willis 2013(95), cited in Zaugg, Korb-Savoldelli et al. 2018(92) the small differences in adherence were not significant, and there was no statistically significant improvement in health resource use with the interventions.

As described in Zhong et al (96), Jarab 2012(97), Khdour 2009(98) and Wei 2013(100, 101) pharmacists provided education in the intervention on patients diagnosed with COPD. It was reported a significant reduction in the risk for hospital admissions in the intervention group in Jarab 2012. The confidence interval for ED visits was wide, showing both a decreased and an increased risk for ED visits and the results were not significant. Khdour 2009 was reported to show a statistically

significant risk reduction for both hospital admissions and ED visits with the intervention, so did Wei 2013 for ED visits.

At an observation study among 4093 patients at a medical unit in Nottingham, UK, the pharmacists found that 6,5 % of the admissions (265 patients) were drug-related morbidity, and that 67 % of the cases were judged to be potentially preventable. Of those 30 % (53 cases) were related to problems with adherence (115). In a study containing 135 008 patients with vascular conditions, there was robust reduction in emergency department visits and inpatient hospital days as a result of adherence(35).

The CHARM-study, which contained 7599 patients, also revealed that admission to hospital for heart failure was lower for the good adherent patients compared to the poor adherent patients, even if the patients received candesartan or placebo. The study concluded that good adherence, even to "non-treatment" (placebo) is one of the strongest variables associated with the outcome(32).

Health care costs

4 studies measured health care costs, but only one of them reported a quantitative result.

In NCT00414817(84-86) cited in Normansell, Kew et al. 2017(116) and Willis 2013(95) cited in Zaugg, Korb-Savoldelli et al. 2018(92), economic analysis and cost were among the outcomes measured, respectively, but the results were not reported. In Margolis 2013, cited in Weeks, George et al. 2016 (37), the costs of medication were higher in the pharmacist prescribing group compared to the usual care group, but it was unclear to which extent. The intervention program was estimated to a total cost of USD 1350 for each patient. Costs were reported as lower in the education group compared to the control group in Khdour 2011(99), cited in Zhong, Ni et al. 2014(96), however the result was not statistically significant.

As reported by WHO, investments in improving adherence are in many cases fully repaid because they lead to savings in in health care utilization. Even general improvement in health outcomes can justify the investment(14). The picture of costs is complex, as it includes both direct costs (e.g. medical care) and indirect costs (e.g. loss of productivity because of days off-work)(42).

In an observational study of 137 277 patients under age 65, where 15 085 of the patients were diagnosed with diabetes, hypercholesterolemia, hypertension or CHF it was shown that high adherence was associated to lower costs. Hospitalization caused the largest medical cost, and all-cause hospitalization rates were significantly lower for all conditions for patients having 80 %-100 %

adherence. Considering this result, it was proposed that change in the hospitalization risk would be the most important impact on cost savings(117).

In a study of 135 008 patients with vascular conditions, pharmacy spending increased simultaneously as adherence increased, and higher adherence consequently led to total health care savings. Among the four conditions their study included, annual medical spending was all significantly lower for adherent patients, reduced by: $ 8 881 in congestive heart failure, $ 4 337 in hypertension, $ 4 413 in diabetes, and $ 1 860 in dyslipidaemia. To achieve both improved adherence and cost savings it was suggested to use interventions that required fewer resources with less expense, such as electronic monitoring devices and pharmacist-led patient counselling(35).

QoL/patient satisfaction

22 studies measured QoL and/or patient satisfaction, and 6 of them reported a statistically significant improvement.

In Nieuwlaat, Wilczynski et al. 2014(13) it was reported no statistically significant improvements in QoL in Holland 2007(71), Murray 2007(73), Niewkerk 2012(75) and Pyne 2011(76), and no statistically significant improvement in neither QoL or patient satisfaction in Bond 2007(67) and Udelson 2009(79). In the same systematic review it was reported no statistically significant positive effect on QoL but on patient satisfaction in Dejesus 2009(69), and Levy 2000(72) and Sadik 2005(77) showed a statistical improvement in QoL for the patients that received education.

In Mathes, Antoine et al 2014(59) it was reported no significant improvement in QoL in Mbuagbaw 2012(61).

As described in Normansell, Kew et al. 2017(82) there was a no-statistically significant result favouring the QoL in the education group in Mehuys 2008(83), also the confidence intervals were broad in Price 2010(87), so the result was not statistically significant, and NCT00414817(84-86) was also reported to have no significant intervention effects.

In Weeks, George et al. 2016(37) QoL and patient satisfaction were reported. There was a higher proportion of patients reporting improved non-statistically significant QoL-results in Bruhn 2013(88), and most of the patients reported satisfaction with pharmacist prescribing , but it was unclear whether the result was statistically significant. The same systematic review reported that the QoL-results favoured the pharmacist management on the physical component, and the usual care on the mental component, the results were non-statistically significant results in Hunt 2008(89). It was

assumed that the patient satisfaction was higher in the intervention group than the usual care group, but it was not provided any quantitative data to support that assumption. In Margolis 2013(91), both the physical and the mental components of QoL were improved in the pharmacist telemonitoring group, but both intervals crossed the point of no effect, so the results were not statistically significant. The patient satisfaction was reported as higher in the intervention group, without any quantitative data to support the assertion.

Al-aqeel et al. 2017 (56) reported that QoL was an outcome in DiIorio 2011(58), but the result was not reported.

Zhong, Ni et al. 2014(96) reported QoL-results in Jarab 2012(97) and Weinberger 2002(102) as not significant, and in Khdour 2009(98) and Wei 2013(100, 101) as statistically significantly improved in the pharmacist groups. The patients receiving pharmacist care reported a significant greater satisfaction at 6 months, but the difference did not sustain on the measurements at 12 months.

Patient satisfaction is a subjective variable, and it is closely attached to the patient's expectations and preferences of care. When measured, the reality can be in contrast to the patients' perceptions, and this needs to be considered when patient satisfaction is used as an outcome in studies for assessing the quality of health care delivery(118), such as adherence interventions. Awareness should also be given when interpreting the results of QoL, since the term is compounded by physical, functional, psychological and social domains perceived by the patient. Also, measures of highly statistically significant treatments effects do not always relate to a change in QoL(119).

Most of the studies measured QoL, and a few measured HRQoL (health related quality of life), anyway, the results were just reported as QoL in this report.