# The impact of issuing longer versus shorter duration prescriptions: a systematic review

Sarah King, Research Fellow, RAND Europe, UK

Céline Miani, Research Associate, Department of Epidemiology & International Public Health, School of Public Health, Bielefeld University, Bielefeld, Germany

Josephine Exley, Senior Analyst, Cambridge Centre for Health Services Research, RAND Europe, UK

Jody Larkin, Research Librarian, RAND Pittsburgh, USA

Anne Kirtley, Insight Research Analyst, Wellcome Trust, London, UK

Rupert A Payne, Consultant Senior Lecturer in Primary Health Care, University of Bristol, UK

**TOTAL WORD COUNT: 2561**

# Abstract

## Background

Long-term conditions place a substantial burden on primary care services, with drug therapy a core aspect of clinical management. The ideal frequency for issuing of repeat prescriptions for these medications is unknown.

## Aim

To examine the impact of longer duration versus shorter (28-day) duration prescriptions.

## Design and Setting

Systematic review of primary care studies (PROSPERO: CRD42015027042**)**

## Method

Scientific and grey literature databases were searched from inception up to 21/10/2015. Eligible studies were randomised controlled trials (RCTs) and observational studies that assessed longer prescriptions (range 2 to 4 months) compared with shorter prescriptions (around 28 days), in patients with stable, chronic conditions being treated in primary care. Outcomes of interest were: health outcomes, adverse events, medication adherence, medication wastage, professional administration time, pharmacists’ time/costs, patient experience, and patient out-of-pocket costs.

## Results

Moderate quality evidence from nine studies suggested that longer prescriptions are associated with increased medication adherence. Evidence from six studies suggested longer prescriptions may increase medication waste, but results were not always statistically significant and were of very low quality. No eligible studies were identified that measured any of the other outcomes of interest, including health outcomes and adverse events.

## Conclusion

There is insufficient evidence for the overall impact of differing prescription lengths on clinical and health service outcomes, although studies do suggest adherence may improve with longer prescriptions. Current UK recommendations to provide shorter prescriptions are not substantiated by the current evidence base.

## How this fits in

Local guidance from many health service commissioners, as well as the UK’s Pharmaceutical Services Negotiating Committee, encourages general practitioners (GPs) to issue shorter prescriptions, typically 28 days in length. This guidance is based on non-systematic review evidence, which was not substantiated by our systematic review. Longer prescriptions lengths for people with stable, chronic conditions could be potentially important to GPs in terms of reducing their workload. It also has the potential to have a positive impact for patients, including improving adherence and thus medication effectiveness, and reducing time, cost and inconvenience.

## Keywords

Prescription length, primary care, repeat prescribing, medication adherence, medication waste

# Introduction

Long-term conditions place a substantial burden on health services, particularly in the primary care setting where they are commonly managed (1). For those patients with relatively stable conditions, drug therapy is usually managed using “repeat prescriptions”, where patients can request a further prescription for a long-term medication without requiring a further consultation with a clinician.

The UK Department of Health advises that the frequency of repeat prescriptions should “balance patient convenience with clinical appropriateness, cost-effectiveness and patient safety”, but does not specify a recommended period (2). However, local guidance from many health service commissioners, as well as the UK’s Pharmaceutical Services Negotiating Committee, encourages general practitioners (GPs) to issue shorter prescriptions, typically 28 days in length (3-6). This guidance is based on non-systematic review evidence of reductions in medicines waste and consequent cost savings (7, 8). One study has reported that shorter prescription lengths may benefit patients by providing better signalling to GPs for treatment discontinuations due to adverse events (9).

However, other work does not support the use of shorter prescriptions, with studies suggesting they may increase health service costs through increased GP administrative workload and pharmacist dispensing costs, increase patient-incurred costs through more frequent trips to the pharmacist (10, 11), and adversely impact upon medication adherence and patient satisfaction (12-14). Prescription lengths also vary considerably between and within countries. For example, the duration of thyroid prescriptions has been found to vary between 28 days in France and 6 months in Australia (15), and prescription durations across all therapeutic areas in the Canadian province of Quebec were approximately half the length of those in the rest of Canada (16).

Given the disparity in evidence and practice, a systematic review was undertaken to examine the impact of primary care physicians issuing longer (three month) versus shorter (28-day) duration prescriptions in patients with stable chronic conditions. The results of a cost analysis and decision analysis model are reported separately (see (17, 18)).

# Methods

We conducted a systematic review following standardised methodology and consistent with PRISMA guidance (19, 20). The protocol is published on the PROSPERO database (registration number CRD42015027042). The protocol and choice of outcomes was drawn up in consultation with lay patient representatives (21).

## Data sources

We searched major scientific and grey literature databases from inception up to 21/10/2015, with no country or language restrictions. Search terms included combinations of the terms prescription, length, and duration, as well as specific time periods. Backward and forward citation searches were conducted. The databases searched and the full search terms are presented in Appendix 1. An updated search in PubMed in July 2017 identified no further articles.

## Eligibility criteria

To be eligible, studies had to be randomised controlled trials (RCTs) or observational studies that compared longer duration prescriptions (including two to four months) with 28-day prescriptions (or around one month) in participants with relatively stable chronic conditions, for example, hypothyroidism, diabetes, cardiovascular disease, and depression. Studies were restricted to primary care settings in middle and high-income countries. Those conducted exclusively within secondary or tertiary care settings were excluded. The studies had to report on one or more of the following outcomes: health outcomes, adverse events, medication adherence, medication wastage, professional administration time, pharmacists’ time/costs, patient experience and patient out-of-pocket costs.

## Data extraction and synthesis

Two independent reviewers screened titles and abstracts identified by the searches, and screened full papers of potentially relevant studies. A third reviewer resolved disagreements. Relevant studies’ characteristics were independently extracted by two reviewers, with a third reviewer checking and comparing the data extraction. An attempt was made to contact study authors for data missing from the identified papers.

Studies were analysed by outcome and by therapeutic area (e.g. lipid lowering medication, diabetic medication) as most of the included studies reported their results in this way. Studies varied in the nature and detail of the drug classification used; where necessary, we categorised medication categories (e.g. statins) into the corresponding therapeutic area (e.g. lipid lowering) to improve consistency across studies.

Within each study, we calculated effect sizes as odds ratios (OR) with 95% confidence intervals (CIs) for dichotomous outcomes, and mean difference (MD) with 95% CIs for continuous outcomes. Where appropriate, standard deviations (SDs) were imputed based on p values (19). Forest plots were generated using RevMan version 5.3. Meta-analyses were not conducted due to clinical heterogeneity between studies. The review was not designed to consider differences between therapeutic areas.

## Risk of bias and quality of evidence

As only observational studies were identified, we assessed risk of bias using The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, although we also considered additional sources of bias (e.g. sample size) (22). Risk of bias was assessed by two reviewers independently, with discrepancies resolved through discussion. The GRADE criteria were used to assess the quality of evidence for each outcome (23).

# Results

Our initial search identified 24,876 records across all databases. After duplicate removal, screening of titles and abstracts, and searching citations, 53 references were considered for full-text evaluation. Thirteen references representing 13 studies met the inclusion criteria (Appendix 2), although 4 were only reported in abstract form but were included because they presented clear outcome data (24-27).

Study characteristics are presented in Appendix 3. All the studies were conducted in the USA, and included nine retrospective cohorts (24-32), three cross-sectional analyses (33-35) and one retrospective before-and-after study (36). Three provided details of the healthcare setting, including a primary care clinic (28), patients seen in primary care, a mental health clinic, inpatient services and an integrated primary care mental health (30), and an internal medicine practice (33). Other studies did not explicitly report being conducted in primary care although we considered them unlikely to have been conducted exclusively in secondary or tertiary care settings (e.g. claims data from community pharmacies). Study populations included patients new to treatment (25-27, 30), patients receiving ongoing care (28, 29, 31), or both (35). Comparisons between prescription lengths were assessed for various therapeutic medication groups, including most commonly lipid-lowering, anti-hypertensive, diabetic, and anti-depressant medications (25-30, 32-36). Most studies compared a 30-day medication supply with a longer period: a 90-day supply (24-26, 29, 32, 35), a 60-day supply (28), or both 31-to-89 days or >90-day supplies (27, 31, 34). Other studies compared 100-day versus 34-day supplies (36), more or less than 90-day supplies (30), and a range of prescription lengths up to 90 days (33).

No eligible studies were identified that measured health outcomes or adverse events. Only one retrospective cohort study measured a risk factor for a health outcome (serum cholesterol was lower in the 60-day compared to 30-day prescription group at 3-years, mean 4.8 [standard deviation 1.2] mmol/l vs. 5.0 [1.4] mmol/l respectively; p=0.003) (28). No eligible studies reported professional administration time, pharmacists’ time/costs, patient experience or out-of-pocket costs other than prescription costs. The most common reported outcomes were medication adherence and wastage.

## Medication adherence

Nine studies reported medication adherence, indirectly estimated using pharmacy claims refill data (Appendix 4) (25, 26, 28, 30-34, 36). Commonly used measures of adherence were the proportion of days covered (PDC = number of days in a given time period “covered” by prescription claims for a particular drug, divided by the number of days in the time period), or the medication possession ratio (MPR = total number of days supplied for all refills of a particular drug in a given time period, divided by the number of days in the time period). We elected not to separate these measures in our analyses (although PDC has been found to provide a more conservative estimate of adherence than the MPR (37)). PDC and MPR were expressed either as the proportion of patients achieving a particular threshold (generally >80%), or the average (mean) value.

Consistent findings were found across all studies. Three cohort studies found prescription lengths shorter than 90 days were associated with poorer adherence across a range of therapeutic areas (including lipid-lowering therapy, antihypertensives, diabetes medication and antidepressants), based on both adherence <80% threshold (odds ratios 0.21 to 0.65, Figure 1) (25, 28, 30). A further three cohort studies found similar associations, based on mean reduction in adherence (mean decrease 0.12 to 0.30, Figure 2) (26, 31, 32). A controlled before-and-after study found shortening of antihypertensive, diabetic and lipid-lowering prescription length from 100 to 34 days was significantly associated (p<0.01) with a 5.3% to 13.2% reduction in those time periods where PDC was ≥80%, and a mean decrease in PDC of 0.034 to 0.080 (no differences were observed for seizure medication or anti-psychotics) (36). In a further cross-sectional study, prescriptions of >90 days were associated with greater adherence (PDC >80%) compared with prescriptions of ≤30 days for drugs affecting the renin-angiotensin system, statins and oral diabetes medications (relative risk 1.61, p<0.001 for each) (34). A second cross-sectional study found each 30-day increment in prescription length (up to 90 days maximum) was associated with a 5.7% increase in mean adherence (p<0.0001), diabetes, anti-hypertensive and lipid-lowering medications (33).

## Medication wastage

Medication wastage was reported in six of the included studies (see Appendix 5) (24, 26, 27, 29, 32). All measures of wastage were indirect, estimated based on pharmacy claims refill data. The majority of these studies defined wastage in a similar manner, such as a ‘switch in medication type within the same clinical class or to the same medication but with a different strength, occurring before the expected refill date’ (29). One study also included discontinuation within its definition (24). Waste was expressed as percentage of days’ supply wasted, percentage of patients with wasted medication, or mean number of days’ supply wasted.

Two retrospective cohort studies assessed percentage of days’ supply wasted, finding only small differences (≤ 1.5%) between different prescription lengths, but neither study reported raw data or statistical comparisons, and additional information could not be obtained from the authors (24, 27).

Three studies evaluated the percentage of patients that wasted medication (27, 32, 35). Odds ratios could be calculated for one retrospective cohort and one cross-sectional study (32, 35). In general, there was non-significant trend for longer prescriptions (90 days vs. 30 days) to be associated with higher proportions of patients with wasted medication; this was statistically significant for lipid-lowering drugs for the study by Taitel only (OR 0.84, 95% CI 0.72-0.98) (32). A third cohort study reported varying patterns across therapeutic areas, but with no statistical analysis and insufficient data to calculate effect sizes (27).

Four studies reported the mean number of days’ supply wasted over one year (26, 29, 32, 35). Effect sizes could not be calculated for one study in which it was unclear if days wasted was standardised between the two prescription groups (35). The remaining studies found evidence that shorter (30 days vs. 90 days) prescriptions were significantly associated with a mean reduction in waste days. Across a range of therapeutic areas, Taitel reported a reduction of between 3.5 and 6.9 days over a 1-year study period (32), and Murphy found a reduction of 0.03 to 0.13 days over a 30-day period (26, 29); Jiang found a mean reduction of -0.1 days averaged for all therapeutic areas (26).

## Risk of bias and quality of evidence

Lack of methodological detail prevented assessment of risk of bias for the four studies presented as abstracts (24-27). One study was classified as having a serious risk of bias due to a small sample size (31) and another was similarly classified as a cut-off point of 84 days was used with no justification provided for this decision (32). The remaining seven studies were considered to have a moderate risk of bias (Appendix 6) (28-30, 33-36). In nine studies, the authors did not explicitly report taking measures to control for selection bias.

In terms of GRADE assessment, the evidence was determined to be of very low quality for all outcomes except adherence outcomes, which were considered to be of moderate quality.

# Discussion

## Summary

This is the first systematic review of evidence comparing the impact of shorter and longer prescriptions on clinical and health service outcomes. We found some evidence from six studies that longer prescriptions are associated with increased medication waste, but the results were not always statistically significant and are of very low quality. We found moderate quality evidence to suggest that longer prescriptions are associated with better adherence. If medication adherence is positively correlated with health outcomes, as seems to be suggested by the wider literature (38, 39), there may be benefits to increasing the length of repeat prescriptions for patients with chronic conditions. However, we found no direct evidence assessing the association between different prescription lengths and health outcomes (including adverse events). Furthermore, although it is important to minimise medication waste, this needs to be balanced against the needs of patients and clinicians’ workloads. However, we found no direct evidence comparing different prescription lengths with differences in health professionals’ administrative time, pharmacists’ time or patient experience.

## Strengths and limitations

Although we followed rigorous methodology, there are limitations to this systematic review. It is possible that some of the studies are not truly representative of primary care, although the findings are generally consistent regardless of setting. Moreover, all of the eligible studies were conducted in the USA and their applicability to UK settings could be limited given differences in health care systems. We may also have missed evidence where prescription lengths were considerably different to our inclusion criteria. Some of the studies differentiated patients receiving new versus existing prescriptions, but we did not consider this in the protocol and not enough studies reported this information to allow a post hoc subgroup analysis. Finally, it was not possible to make comparisons of effect sizes between different therapeutic areas.We have recently conducted an analysis within routine UK primary care health records, not included in this systematic review, which addresses some of these concerns (17).

A key issue with all of the studies was their use of indirect, proxy measures for both adherence and waste, based on administrative prescription refill data. The two key adherence measures used were PDC and MPR, which may introduce bias in favour of longer prescriptions as well as underestimating true adherence (40, 41). Similar concerns can be raised about the estimation of waste. Nevertheless, a review of such approaches has determined that indirect measures still have value (42).

None of the studies explored why adherence may differ between prescription lengths. Reasons for medication nonadherence are often complex, and can be both intentional and unintentional (43). Longer prescription lengths may overcome barriers to unintentional adherence, such as enabling patients to follow a regular medicine regimen or reducing logistical barriers such as visits to the pharmacy (28, 31, 33). However, given the observational nature of the studies, there is a risk of systematic differences, with longer prescriptions issued to patients considered more adherent by the prescriber, those having more stable illness (30), or those of non-white ethnicity (44).

We identified only one study that showed a beneficial association between longer prescriptions and improved clinical outcome (28). There was a lack of research examining the association between prescription duration and other outcomes, although some non-comparative evidence exists for shorter prescriptions being considered inconvenient and disempowering, and causing patient dissatisfaction and anxiety (13, 14),(45).

## Implications for research and practice

This review has found that medication adherence may be associated with longer prescription durations, which in theory may translate to clinical benefit. The evidence that such prescriptions also lead to increased waste is, however, very weak. Current UK policy recommending the provision of shorter prescriptions is not substantiated by the current evidence base, and further research is required to evaluate the clinical, health service and economic impact of differing prescription lengths.

This research was funded by the NIHR HTA contract number: 14/159/07.

All work was conducted and analysed independently of the funder. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Ethical approval was not required for this research.

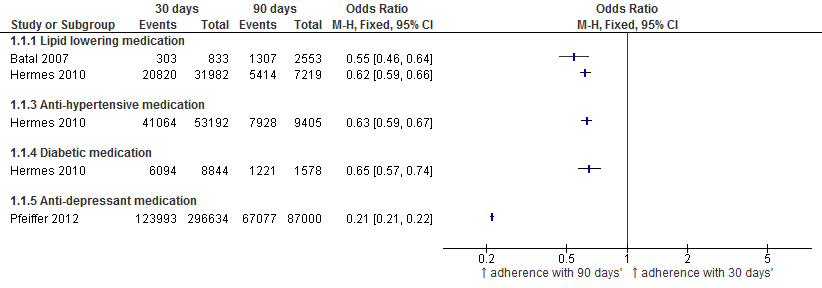
Competing interests: None declared. All authors have completed the unified competing interest form at www.icmje.org/coi\_disclosure.pdf (available on request from the corresponding author).

**Acknowledgments**

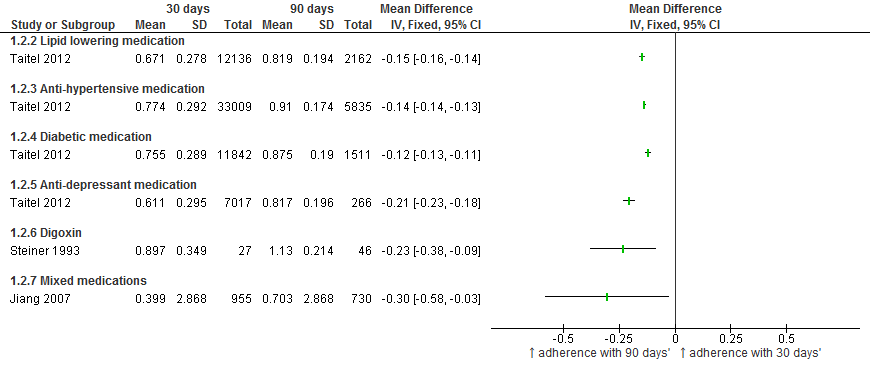
We would like to thank the following people who made invaluable suggestions during the review process: Catherine Meads, Anthony Avery, Molly Morgan Jones, and Adam Martin. We would also like to thank the peer reviewers for their comments on this paper.

# Figure 1 Medication adherence

A. Proportion of patients with ≥ 80% medication adherence

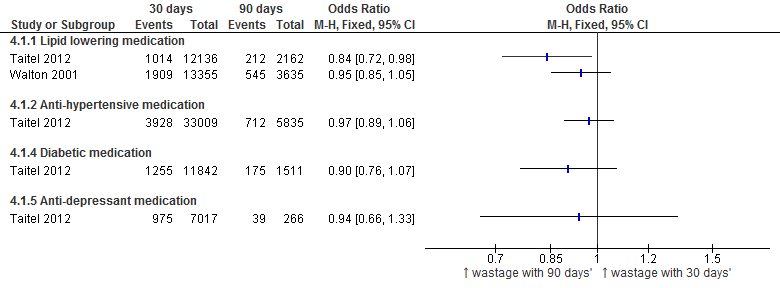


B. Mean medication adherence

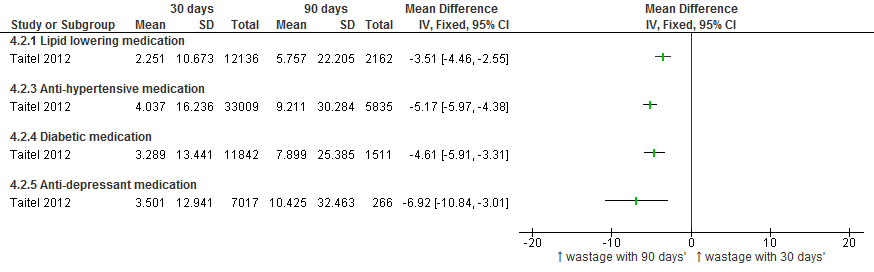


# Figure 2 Wasted medication

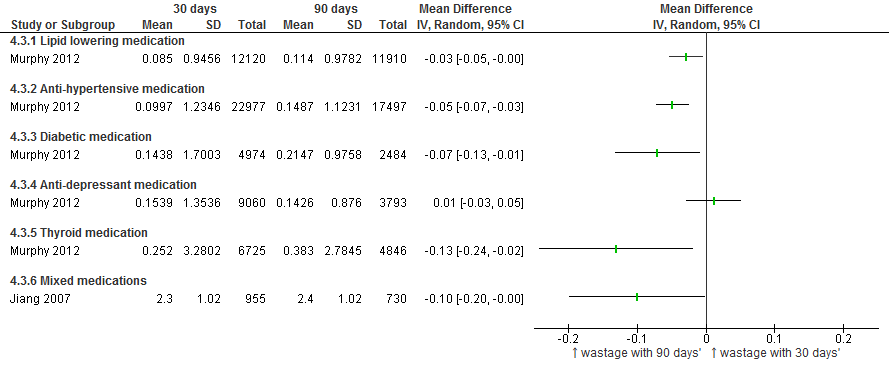
A. Percentage of patients with wasted medication



B. Mean days with wasted medication over the study period



C. Mean days with wasted medication per 30 days (rate data)



# References

1. Baird B, Charles A, Honeyman M, Maguire D, Das P. Understanding pressures in general practice: King's Fund; 2016.

2. Department of Health. Publications policy and guidance. Repeat prescribing systems. URL: <http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/Browsable/DH_4892136> (last accessed June 2017). 2011.

3. Pharmaceutical Services Negotiating Committee. Medicines wastage and 28 day prescribing guidance. London: Pharmaceutical Services Negotiating Committee; 2007.

4. NHS Cambridgeshire. Repeat Medication for 28 Days. Cambridge: Cambridgeshire Primary Care Trust; 2009.

5. NHS North East Essex. Prescribing interval policy. North East Essex PCT; 2010.

6. NHS Dorset Clinical Commissioning Group. Medicines Code Chapter 15: Policy for Repeat Prescribing and Medication Review. Dorset Clinical Commissioning Group; 2013.

7. Hawksworth GM, Wright DJ, Chrystyn H. A day to day analysis of the unwanted medicinal products returned to community pharmacies for disposal. Journal of Social and Administrative Pharmacy. 1996;13(4):215-22.

8. Pharmaceutical Services Negotiating Committee. PSNC Briefing 086/13: Medicines wastage and prescription duration. London: Pharmaceutical Services Negotiating Committee; 2013.

9. Sun A, Kirby B, BLack C, Helms P, Bennie M, McLay J. Unplanned medication discontinuation as a potential pharmacovigilance signal: a nested young person cohort study. BMC Pharmacol Toxocol. 2014;15(1):11.

10. White KG. UK interventions to control medicines wastage: a critical review. International Journal of Pharmacy Practice. 2010;18:131-40.

11. Domino ME, Olinick J, Sleath B, Leinwand S, Byrns PJ, Carey T. Restricting patients' medication supply to one month: saving or wasting money? American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2004;61(13):1375-9.

12. Wong MC, Tam WW, Wang HH, Cheung CS, Tong EL, Cheung N, et al. Duration of initial antihypertensive prescription and medication adherence: A cohort study among 203,259 newly diagnosed hypertensive patients. International Journal of Cardiology. 2015;182:503-8.

13. Mitchell AL, Hickey B, Hickey JL, Pearce SH. Trends in thyroid hormone prescribing and consumption in the UK. BMC public health. 2009;9:132.

14. Wilson PM, Kataria N, McNeilly E. Patient and carer experience of obtaining regular prescribed medication for chronic disease in the English National Health Service: a qualitative study. BMC health services research. 2013;13(1):192.

15. British Thyroid Foundation. Precription Lengths: Prescribing Trends Around the World. URL: <http://www.btf-thyroid.org/projects/prescription-lengths/227-prescribing-trends-around-the-world> (last accessed April 2017). BTF News. 2009(70).

16. Smolina K, Morgan S. The Drivers of Overspending on Prescription Drugs in Quebec. Healthcare Policy. 2014;10(2):19-26.

17. Doble B, Payne R, Harshfield A, Wilson ECF. Retrospective, multicohort analysis of the Clinical Practice Research Datalink (CPRD) to determine differences in the cost of medication wastage, dispensing fees and prescriber time of issuing either short (&lt;60 days) or long (≥60 days) prescription lengths in primary care for common, chronic conditions in the UK. BMJ Open. 2017;7(12).

18. Martin A, Payne R, Wilson ECF. Long term costs and health consequences of issuing shorter duration prescriptions for patients with chronic health conditions in the English NHS. forthcoming.

19. Higgins J, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [updated March 2011]. URL: <http://handbook.cochrane.org> (last accessed May 2016): The Cochrane Collaboration; 2011.

20. Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. Ann Intern Med. 2009;15(4):W65-W94.

21. Primary Care Unit University of Cambridge. Patient and Public Involvement URL: <http://www.phpc.cam.ac.uk/pcu/research/ppi/> (last accessed June 2017).

22. Sterne J, Hernán M, Reeves B, Savović J, Berkman N, Viswanathan M, et al. The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool. URL:

<https://53e94a67-a-62cb3a1a-s-sites.googlegroups.com/site/riskofbiastool/ROBINS-I%20tool%20template%207mar2016.pdf?attachauth=ANoY7coM9HN73gcazfyKnRjYWZa9FkxQd1w-Wk50RbYv9_7RRWwudlKJ0v-BkImmSXTMKXjISpyPMQpIToL4WAWjgpe4cemSAy-ZEThe1cGyIqxiv4kRDYXPPE4CP09bCfBJwV9jJukvvbsSd0uWz5aCEBEwC3uC8lNcY9Z0cHw52pxrX0WJyLIhWVcnxwLUvHFBjSRZ8mX3Lm6-sJrXe-iEpEvvPy66UbGOugChkfqsfXgDgc2Q6mKrhAk97TOkoILohXUQ8jHm&attredirects=0> (last accessed July 2016). 2016.

23. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

24. Faris RJ, Filipek TM, Tang J, Wanta TM, Takagi MA, Steinberg SC. A retrospective comparative analysis of medication waste from day supply plan design in specialty pharmacy. Journal of Managed Care Pharmacy. 2010;16(7):516.

25. Hermes M, Gleason PP, Starner CI. Adherence to chronic medication therapy associated with 90-day supplies compared with 30-day supplies. Journal of Managed Care Pharmacy. 2010;16(2):141-2.

26. Jiang J, Khandelwal N, Lee K. Comparing medication adherence and wastage among three different retail programs. Value in Health. 2007;10(3):A29.

27. Ryvkin M, Garavaglia S. Wasted medication: How big is the problem? Value in Health. 2009;12(3):A82.

28. Batal HA, Krantz MJ, Dale RA, Mehler PS, Steiner JF. Impact of prescription size on statin adherence and cholesterol levels. BMC Health Serv Res. 2007;7:175.

29. Murphy P, Kahndelwal N, Duncan I. Comparing medication wastage by fill quantity and fulfillment channel. Am J Pharm Benefits. 2012;4(5):e166-e71.

30. Pfeiffer PN, Szymanski BR, Valenstein M, McCarthy JF, Zivin K. Trends in antidepressant prescribing for new episodes of depression and implications for health system quality measures. Medical care. 2012;50(1):86-90.

31. Steiner J, Robbins L, Roth S, Hammond S. The effect of prescription size on acquisition of maintenance medications. J Gen Intern Med. 1993;8(3):6-10.

32. Taitel M, Fensterheim L, Kirkham H, Sekula R, Duncan I. Medication days' supply, adherence, wastage, and cost among chronic patients in Medicaid. Medicare & Medicaid Research Review. 2012;2(3):E1-E13.

33. Schectman JM, Bovbjerg VE, Voss JD. Predictors of medication-refill adherence in an indigent rural population. Medical care. 2002;40(12):1294-300.

34. Schmittdiel J, Nichols G, Dyer W, Steiner JF, Karter A, Raebel M. Health care system-level factors associated with performance on Medicare STAR adherence metrics in a large, integrated delivery system. Medical care. 2015;53:332-37.

35. Walton S, Arondekar B, Johnson N, Schumock G. A model for comparing unnecessary costs associated with various prescription fill-quantity policies: illustration using VA data. J Managed Care Pharm. 2001:384-90.

36. Domino ME, Martin BC, Wiley-Exley E, Richards S, Henson A, Carey TS, et al. Increasing time costs and copayments for prescription drugs: an analysis of policy changes in a complex environment. Health services research. 2011;46(3):900-19.

37. Martin BC, Wiley-Exley EK, Richards S, Domino ME, Carey TS, Sleath BL. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. Ann Pharmacother. 2009;43(1):36-44.

38. Dragomir A, Côté R, White M, Lalonde L, Blais L, Bérard A, et al. Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. Value Health. 2010;13(1):87-94.

39. Perreault S, Ellia L, Dragomir A, Côté R, Blais L, Lalonde L. Effect of statin adherence on cerebrovascular disease in primary prevention. Am J Med. 2009;122(7):647-55.

40. Christensen DB, Williams B, Goldberg HI, Martin DP, Engelberg R, P LJ. Assessing compliance to antihypertensive medications using computer-based pharmacy records. Medical care. 1997;35(11):1164-70.

41. Lam WY, Fresco P. Medication adherence measures: an overview. Biomed Res Int. 2015;2015(217047):-.

42. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. Journal of Clinical Epidemiology. 1997;50(1):105-16.

43. Payne R. Understanding can lead to a solution for non-adherence. Prescriber. 2014;25(22):27-8.

44. Rabbani A, Alexander GC. Cost savings associated with filling a 3-month supply of prescription medicines. Applied health economics and health policy. 2009;7(4):255-64.

45. Addison's Disease Self Help group. Letter to Professor Gilmore on review of prescription charges for those with long-term conditions. URL: <http://www.addisons.org.uk/comms/media/gilmore1.pdf> (last accessed July 2016). 2009.

# Appendix 1: Search Strategy

## Scientific and related database searches

PubMed, Embase, CINAHL, Web of Science, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment Database (HTA), NIHR Health Technology Assessment, NICE Technology appraisals,

### Medline (PubMed)

Prescription length\*[title/abstract] OR prescription duration\*[title/abstract] OR medication duration\*[title/abstract] OR “medication length”[title/abstract] OR “length of prescription”[title/abstract] OR “length of prescriptions”[title/abstract] OR “duration of prescription”[title/abstract] OR “duration of prescriptions”[title/abstract] OR “durations of prescriptions”[title/abstract] OR “drug prescribing”[title/abstract] OR “multiple drug prescriptions”[title/abstract] OR prescribing pattern\*[title/abstract] OR prescription pattern\*[title/abstract] OR prescribing behavior\*[title/abstract] OR prescribing behaviour\*[title/abstract] OR prescribing practice\*[title/abstract] OR prescribing standard\*[title/abstract] OR (installment[title/abstract] AND dispensing[title/abstract]) OR repeat prescri\*[title/abstract] OR “repeat dispensing”[title/abstract] OR prescribing interval\*[title/abstract] OR prescription interval\*[title/abstract] OR “28 day supply”[Title/abstract] OR “34 day supply”[title/abstract] OR ("28 day"[title/abstract] AND ("drug supply"[title/abstract] OR prescribing[title/abstract] OR prescription[title/abstract])) OR “56 day supply”[title/abstract] OR ("56 day"[title/abstract] AND ("drug supply"[title/abstract] OR prescribing[title/abstract] OR prescription[title/abstract])) OR “28 day drug limit”[title/abstract] OR “56 day drug limit”[title/abstract] OR “one month prescription”[title/abstract] OR “one month prescriptions”[title/abstract] OR “1 month prescription”[title/abstract] OR “1 month supply”[title/abstract] OR “one month supply”[title/abstract] OR “3 month prescriptions”[title/abstract]OR “three month prescription”[title/abstract] OR “three month prescriptions”[title/abstract] OR “3 month prescription”[title/abstract] OR “3 month supply”[title/abstract] OR “three month supply”[title/abstract] OR “90 day supply”[title/abstract] OR “30 day supply”[title/abstract] OR “60 day supply”[title/abstract] OR dosage unit\*[title/abstract] OR “prescription standardization”[title/abstract] OR “prescription standardisation”[title/abstract] OR prescription restriction\*[title/abstract] OR prescribing restriction\*[title/abstract] OR “restricting prescriptions”[title/abstract] OR “restricting medication”[title/abstract] OR medication restriction\*[title/abstract] OR dispensing restriction\*[title/abstract] OR prescribing trend\*[title/abstract] OR prescription trend\*[title/abstract] OR dispensing trend\*[title/abstract] OR “trends in dispensing”[title/abstract] OR "trends in prescribing"[title/abstract] OR prescription suppl\*[title/abstract] OR medication suppl\*[title/abstract] OR term prescription\*[title/abstract] OR ((short course\*[title/abstract] OR long course\*[title/abstract]) AND (prescription\*[title/abstract] OR medication\*[title/abstract])) OR “short prescription”[title/abstract] OR “long prescription”[title/abstract] OR “short prescriptions”[title/abstract] OR “long prescriptions”[title/abstract] OR standardized prescri\*[title/abstract] OR “standardised prescription”[title/abstract] OR “standardised prescribing”[title/abstract] OR (Standardization[title/abstract] AND (prescribing[title/abstract] OR prescription\*[title/abstract])) OR (Standardisation[title/abstract] AND (prescribing[title/abstract] OR prescription\*[title/abstract])) OR individualized prescri\*[title/abstract] OR individualised prescri\*[title/abstract] OR (individualization[title/abstract] AND prescrib\*[title/abstract]) OR (individualisation[title/abstract] AND prescrib\*[title/abstract]) OR Drug Prescriptions/trends OR Drug Prescriptions/supply and distribution

**Results: 8,242 – animal = 8,207**

### Embase

(prescription\* NEAR/2 length\*):ti,ab OR (prescription\* NEAR/2 duration\*):ti,ab OR (medication\* NEAR/2 duration\*):ti,ab OR (medication\* NEAR/2 length\*):ti,ab OR “drug prescribing”:ti,ab OR “multiple drug prescriptions”:ti,ab OR (prescri\* NEXT/1 pattern\*):ti,ab OR (prescribing NEXT/1 behaviour\*):ab,ti (prescribing NEXT/1 behavior\*):ab,ti OR (prescribing NEXT/1 practice\*):ab,ti OR (prescribing NEXT/1 standard\*):ab,ti OR “installment dispensing”:ti,ab OR (repeat NEXT/1 prescri\*):ti,ab OR (repeat NEXT/1 dispens\*):ti,ab OR (prescri\* NEXT/1 interval\*):ti,ab OR (prescri\* NEXT/1 interval\*):ti,ab OR ((28 OR 30 OR 34 OR 56 OR 60 OR 90) NEXT/1 day NEXT/1 supply):ti,ab OR ((28 OR 30 OR 34 OR 56 OR 60 OR 90) NEXT/1 day NEXT/1 drug NEXT/1 supply):ti,ab OR ((28 OR 30 OR 34 OR 56 OR 60 OR 90) NEXT/1 day NEXT/1 prescri\*):ti,ab OR ((28 OR 30 OR 56 OR 60 OR 90) NEXT/1 day NEXT/1 drug NEXT/1 limit):ti,ab OR “one month prescription”:ti,ab OR “1 month prescription”:ti,ab OR “one month supply”:ti,ab OR “1 month supply”:ti,ab OR (3 NEXT/1 month NEXT/1 prescription\*):ti,ab OR (three NEXT/1 month NEXT/1 prescription\*):ti,ab OR “3 month supply”:ti,ab OR “three month supply”:ti,ab OR (dosage NEXT/1 unit\*) OR “prescription standardization”:ti,ab OR “prescription standarisation”:ti,ab OR (prescri\* NEAR/1 restrict\*):ti,ab OR (medication\* NEAR/1 restrict\*):ti,ab OR (dispensing NEXT/1 restrict\*):ti,ab OR (prescri\* NEAR/2 trends):ti,ab OR (dispensing NEAR/2 trends):ti,ab OR ((prescription OR medication) NEXT/1 suppl\*):ti,ab OR ((short OR long) NEXT/1 (course OR term) NEXT/1 (prescription\* OR medication\*)):ti,ab OR ((short OR long) NEXT/1 prescription\*):ti,ab OR ((standardised OR standardized OR standardization OR standardisation) NEXT/2 prescri\*):ti,ab OR ((individualized OR individualized OR individualization OR individualisation) NEXT/1 prescri\*):ti,ab

**Results: 6,266 – duplicates/animal = 3,600**

### CINAHL

TI “prescription length\*” OR AB “prescription length\*” OR TI "prescription duration\*" OR AB "prescription duration\*" OR TI "length\* of prescription\*" OR AB "length\* of prescription\*" OR TI "duration\* of prescription\*" OR AB "duration\* of prescription\*" OR TI "drug prescribing" OR AB "drug prescribing" OR TI "multiple drug prescriptions" OR AB "multiple drug prescriptions" OR TI "prescri\* pattern\*" OR AB "prescri\* pattern\*" OR TI "prescribing behavior\*" OR AB "prescribing behavior\*" OR TI "prescribing behaviour\*" OR AB "prescribing behaviour\*" OR TI "prescribing practice\*" OR AB "prescribing practice\*" OR TI "prescribing standard\*" OR AB "prescribing standard\*" OR TI "installment dispensing" OR AB "installment dispensing" OR TI "repeat prescri\*" OR AB "repeat prescri\*" OR TI "28 day supply" OR AB "28 day supply" OR TI "30 day supply" OR AB "30 day supply" OR TI "30 day drug supply" OR AB "30 day drug supply" OR TI "28 day drug supply" OR AB "28 day drug supply" OR TI "34 day drug supply" OR AB "34 day drug supply" OR TI "34 day supply" OR AB "34 day supply OR TI "28 day prescri\*" OR AB "28 day prescri\*" OR TI "30 day prescri\*" OR AB "30 day prescri\*" OR TI "34 day prescri\*" OR AB "34 day prescri\*" OR TI "28 day drug limit\*" OR AB "28 day drug limit\*" OR TI "30 day drug limit\*" OR AB "30 day drug limit\*" OR TI "34 day drug limit\*" OR AB "34 day drug limit\*" OR TI "56 day supply" OR AB "56 day supply" OR TI "56 day drug supply" OR AB "56 day drug supply" OR TI "56 day prescri\*" OR AB "56 day prescri\*" OR TI "56 day drug limit\*" OR AB "56 day drug limit\*" OR TI "60 day supply" OR AB "60 day supply" OR TI "60 day drug supply" OR AB "60 day drug supply" OR TI "60 day prescri\*" OR AB "60 day prescri\*" OR TI "60 day drug limit\*" OR AB "60 day drug limit\*" OR TI "90 day supply" OR AB "90 day supply" OR TI "90 day drug supply" OR AB "90 day drug supply" OR TI "90 day prescri\*" OR AB "90 day prescri\*" OR TI "90 day drug limit\*" OR AB "90 day drug limit\*" TI "one month prescription\*" OR AB "one month prescription\*" OR TI "1 month prescription\*" OR AB "1 month prescription\*" OR TI "1 month supply" OR AB "1 month supply" OR TI “one month supply” OR AB “one month supply” OR TI "three month prescription\*" OR AB "three month prescription\*" OR TI "3 month prescription\*" OR AB "3 month prescription\*" OR TI "3 month supply" OR AB "3 month supply" OR TI "three month supply" OR AB "three month supply" OR TI "dosage unit\*" AND AB "dosage unit\*" OR TI "prescription standardization\*" OR AB "prescription standardization\*" OR TI "prescription standardisation\*" OR AB "prescription standardisation\*" OR TI "prescri\* restriction\*" OR AB "prescri\* restriction\*" OR TI "restricting prescription\*" OR AB "restricting prescription\*" OR TI "restricting medication\*" OR AB "restricting medication\*" OR TI "medication restriction\*" OR AB "medication restriction\*" OR TI "dispensing restriction\*" OR AB "dispensing restriction\*" OR TI "prescri\* trend\*" OR AB "prescri\* trend\*" OR TI "dispensing trend\*" OR AB "dispensing trend\*" OR TI "trends in dispensing" OR AB "trends in dispensing" OR TI "trends in prescribing" OR AB "trends in prescribing" OR TI "prescription suppl\*" OR AB "prescription suppl\*" OR TI "medication suppl\*" OR AB "medication suppl\*" OR TI "term prescription\*" OR AB "term prescription\*" OR TI "short course prescription\*" OR AB "short course prescription\*" OR TI "long course prescription\*" OR AB "long course prescription\*" OR TI "short course medication\*" OR AB "short course medication\*" OR TI "long course medication\*" OR AB "long course medication\*" OR TI "short prescription\*" OR AB "short prescription\*" OR TI "long prescription\*" OR AB "long prescription\*" OR TI "standardized perscri\*" OR AB "standardized perscri\*" OR TI "standardised perscri\*" OR AB "standardised perscri\*" OR TI "standarization of prescri\*" OR AB "standarization of prescri\*" OR TI "standarisation of prescri\*" OR AB "standarisation of prescri\*" OR TI "individualized prescri\*" OR AB "individualized prescri\*" OR TI "individualised prescri\*" OR AB "individualised prescri\*" OR TI "individualization prescri\*" OR AB "individualization prescri\*" OR TI "individualisation prescri\*" OR AB "individualisation prescri\*"   
**Results: 1,737 - duplicates = 367**

### Web of Science

Refined by: [excluding] DOCUMENT TYPES: ( LETTER OR NEWS ITEM OR EDITORIAL MATERIAL OR BOOK CHAPTER OR NOTE OR BOOK REVIEW OR DISCUSSION ) AND [excluding] WEB OF SCIENCE CATEGORIES: ( OPERATIONS RESEARCH MANAGEMENT SCIENCE OR VETERINARY SCIENCES OR COMPUTER SCIENCE ARTIFICIAL INTELLIGENCE OR MATHEMATICAL COMPUTATIONAL BIOLOGY OR COMPUTER SCIENCE THEORY METHODS OR METEOROLOGY ATMOSPHERIC SCIENCES OR MECHANICS OR FORESTRY OR TELECOMMUNICATIONS OR MATHEMATICS OR MATERIALS SCIENCE MULTIDISCIPLINARY OR ECOLOGY OR FOOD SCIENCE TECHNOLOGY OR AUTOMATION CONTROL SYSTEMS OR ASTRONOMY ASTROPHYSICS ) AND [excluding] WEB OF SCIENCE CATEGORIES: ( STATISTICS PROBABILITY OR POLYMER SCIENCE OR MATHEMATICS INTERDISCIPLINARY APPLICATIONS OR AGRICULTURE DAIRY ANIMAL SCIENCE OR PLANT SCIENCES OR PHYSICS PARTICLES FIELDS OR BIOCHEMISTRY MOLECULAR BIOLOGY OR OCEANOGRAPHY OR ENGINEERING MULTIDISCIPLINARY ) AND [excluding] RESEARCH AREAS: ( WATER RESOURCES OR MATERIALS SCIENCE OR MINING MINERAL PROCESSING OR METALLURGY METALLURGICAL ENGINEERING OR MATHEMATICS ) AND [excluding] WEB OF SCIENCE CATEGORIES: ( PHYSICS FLUIDS PLASMAS OR ENERGY FUELS OR AGRICULTURE MULTIDISCIPLINARY ) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

TS=(prescription\* NEAR/2 length\*) OR TS=(prescription\* NEAR/2 duration\*) OR TS=("duration of medication\*") OR TS=("length\* of medication\*") OR TS=(“drug prescribing”) OR TS=(“multiple drug prescriptions”) OR TS=("prescription pattern\*") OR TS=("prescribing pattern\*") OR TS=(“prescri\* pattern\*”) OR TS=("prescribing behavior\*") OR TS=("prescribing behaviour\*") OR TS=("prescription behavior\*") OR TS=("prescription behaviour\*") OR TS=(“prescri\* practice\*”) OR TS=("prescription standard\*") OR TS=("prescribing standard\*") OR TS=(“installment dispensing”) OR TS=(“repeat dispens\*”) OR TS=("repeat\* prescription\*") OR TS=("repeat\* prescribing\*") OR TS=("prescribing interval\*") OR TS=("prescription interval\*") OR TS=(“28 day supply”) OR TS=(“30 day supply”) OR TS=(“34 day supply”) OR TS=(“56 day supply”) OR TS=(“60 day supply”) OR TS=(“90 day supply”) OR TS=(“28 day drug supply”) OR TS=(“30 day drug supply”) OR TS=(“34 day drug supply”) OR TS=(“56 day drug supply”) OR TS=(“60 day drug supply”) OR TS=(“90 day drug supply”) OR TS=(“28 day prescri\*”) OR TS=(“30 day prescri\*”) OR TS=(“34 day prescri\*”) OR TS=(“56 day prescri\*”) OR TS=(“60 day prescri\*”) OR TS=(“90 day prescri\*”) OR TS=(“28 day drug limit\*”) OR TS=(“30 day drug limit\*”) OR TS=(“34 day drug limit\*”) OR TS=(“56 day drug limit\*”) OR TS=(“60 day drug limit\*”) OR TS=(“90 day drug limit\*”) OR TS=(“one month prescription”) OR TS=(“1 month prescription”) OR TS=(“one month supply”) OR TS=(“1 month supply”) OR TS=(“three month prescription\*”) OR TS=(“3 month prescription\*”) OR TS=(“three month supply”) OR TS=(“3 month supply”) OR TS=(“dosage unit\*”) OR TS=(“prescription standardization”) OR TS=(“prescription standardisation”) OR TS=(prescri\* NEAR/1 restrict\*) OR TS=(medication\* NEAR/1 restrict\*) OR TS=(“dispensing restrict\*”) OR TS=(dispensing NEAR/2 trends) OR TS=(prescri\* NEAR/2 trends) OR TS=(“prescription suppl\*”) OR TS=(“medication suppl\*”) OR TS=(“short term prescription\*”) OR TS=(“short term medication\*”) OR TS=(“short course prescription\*”) OR TS=(“short course medication\*”) OR TS=(“long term prescription\*”) OR TS=(“long term medication\*”) OR TS=(“long course prescription\*”) OR TS=(“long course medication\*”) OR TS=(“short prescription\*”) OR TS=(“long prescription\*”) OR TS=((standardized OR standardised OR standardization OR standardisation) NEAR/2 prescri\*) OR TS=((individualized OR indvidualised OR individualization OR individualization) NEAR/1 (prescription\* OR prescribing))

**8,592 – duplicates/animal: 3,002**

### Cochrane

“length of prescription”:ti,ab OR “prescription length”:ti,ab OR “prescription duration”:ti,ab OR “drug prescribing”:ti,ab OR “multiple drug prescription\*”:ti,ab OR “prescri\* pattern”:ti,ab OR “prescribing behavior”:ti,ab OR “prescri practice”:ti,ab OR “prescri\* standard\*”:ti,ab OR “repeat dispens\*”:ti,ab OR “repeat prescri\*”:ti,ab OR “prescri\* interval\*”:ti,ab OR "28 day supply":ti,ab OR "30 day supply":ti,ab or "34 day supply":ti,ab OR "60 day supply":ti,ab or "90 day supply":ti,ab OR "28 day prescri\*":ti,ab OR "30 day prescri\*":ti,ab or "34 day prescri\*":ti,ab OR "60 day prescri\*":ti,ab or "90 day prescri\*":ti,ab or “56 day prescri\*”:ti,ab OR “one month prescription”:ti,ab OR “1 month prescription”:ti,ab OR “one month supply”:ti,ab OR “1 month supply”:ti,ab OR “three month prescription”:ti,ab OR “3 month prescription”:ti,ab OR “3 month supply”:ti,ab OR “three month supply”:ti,ab OR “dosage unit\*”:ti,ab OR “prescription standardization”:ti,ab OR “prescri\* restriction\*”:ti,ab OR “medication restrict\*”:ti,ab OR “dispensing restriction\*”:ti,ab OR “dispensing NEAR/2 trend\*”:ti,ab OR “prescription NEAR/2 trend\*” OR “medication supply”:ti,ab OR “medication supplies”:ti,ab OR “short term prescription\*”:ti,ab OR “long term prescription\*”:ti,ab OR “prescription suppl\*”:ti,ab OR ((standardized OR standardised OR standardization OR standardisation) NEAR/2 prescri\*) OR ((individualized OR indvidualised OR individualization OR individualization) NEAR/1 (prescription\* OR prescribing))

**After duplicates: 69**

### NICE

“length of prescription” OR “prescription length” OR “medication length” OR “prescription trends” OR “medication trends” OR “multiple prescriptions” OR “30 day supply” OR “60 day supply” OR “90 day supply” OR “one month supply” OR “three month supply” OR “prescription supply” OR “medication supply” OR “short term prescription” OR “long term prescription” OR “standardised prescription” OR “individualised prescription” OR “prescribing behaviour”

\*\*added **5 records**.

### Total

15,250 (NO year limits)

## Grey literature searches

NYAM Grey Literature Report, OAISTER, OpenGrey

### NYAM

prescribing patterns; prescription length; one month supply; 28 day supply; length of prescription; multiple drug prescription; dispensing restriction; prescribing trends; prescribing behavior; individualized prescribing; individualized prescription; month supply;

### Oaister

Ti: Prescribing patterns; ti: length of prescription; ti: prescription standardization; ti: dispensing regulation; ti: 30 day supply; ti: repeat dispensing; ti: medication prescription; ti: individualized prescri\*; ti: multiple drug prescri\*; ti: short term prescri\*; ti: long term prescri\*; ti: prescription trends; ti: prescribing trends;

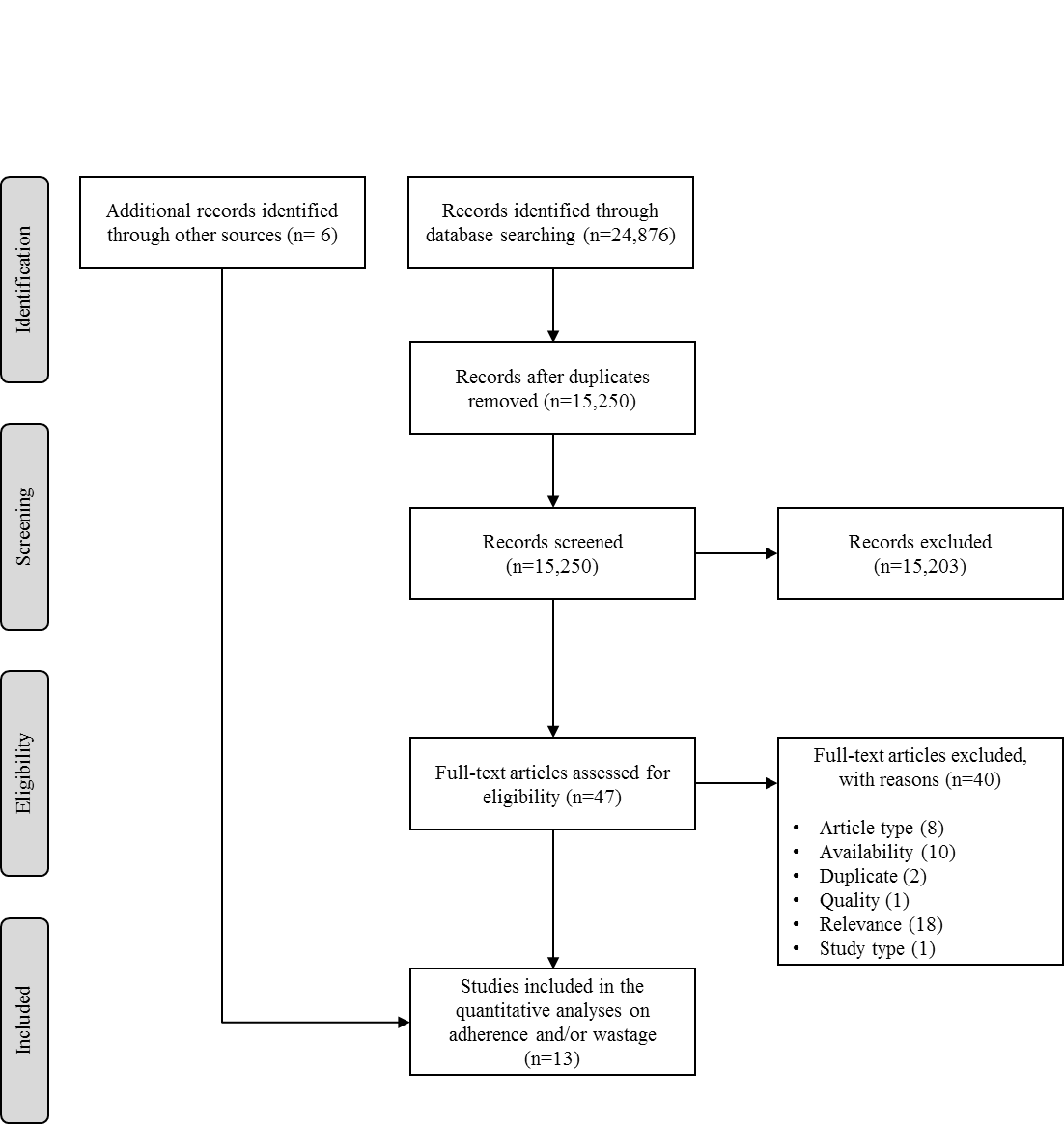
### OpenGrey

“prescribing patterns”; “prescription length”; “prescription standardization”; “dispensing regulations”; “prescription trends”; “prescription patterns”; “individualized prescri\*”; “prescribing trends”; “28 day supply”; “multiple prescriptions”;

### Total

14

# Appendix 2: PRISMA flow chart



# Appendix 3: Characteristics of included studies

| **Reference, country, and study design** | **Aim** | **Participants** | **Setting** | **Medication evaluated** | **Comparison** | **Total sample size**  **(patients unless otherwise stated)** | **Outcomes measured** | **Study length** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Batal 2007(28)  USA  Retrospective cohort | To determine the effect of prescription size on patients' adherence to hyperlipidaemia therapy. | Patients receiving ongoing care and medication for hyperlipidaemia | Primary care clinic serving a predominantly minority and indigent population | * Lipid lowering agents (statins) | 60-day supply of medication (based on modal supply of more than 45 days) compared to 30 day supply (based on modal supply of less than 45 days) | 3,386 | * Adherence * Health (risk only) | 3 years |
| Domino 2011(36)  USA  Retrospective before and after controlled study with a cost consequence analysis | To estimate the effect of two separate policy changes in the North Carolina Medicaid program: (1) reduced prescription lengths from 100 to 34 days' supply, and (2) increased co-payments for brand name medications. | Adult Medicaid recipients who use medications for chronic conditions | Not explicitly reported; claims data from two centres for Medicare and Medicaid Services | * Anti-depressants * Anti-hypertensives * Anti-psychotics * Diabetic medication (sulfonylureas) * Seizure disorder medications * Lipid lowering agents (statins) | Reduced prescription length from 100 days to 34 days | 268,050 | * Adherence * Cost | 18 months |
| Faris 2010(24)  USA  \*Abstract  Retrospective cohort | To determine the impact of days' supply on waste. To compare medication waste rates between patients with a 90-day supply and those with a 30-day supply in 4 speciality therapeutic categories. | Patients with four specialty therapeutic categories: multiple sclerosis, rheumatoid arthritis, oncology and growth hormone | Not explicitly reported | Medications for:   * Multiple sclerosis * Rheumatoid arthritis * Oncology * Growth hormone | 90-day supply compared to 30-day supply | Not reported | * Wastage | 21 months (360 day study period and 270-day washout period (to determine drop off) |
| Hermes 2010(25)  \*Abstract  USA  Retrospective cohort | To compare adherence within three chronic medication classes by days’ supply and evaluate potential adherence predictors. | Members with a first claim | Not explicitly reported | * Anti-hypertensives * Diabetic medications * Lipid lowering agents | 90-day supply compared to 30-day supply | at 270 days: 183,666  at 540 days: 112,220 | * Adherence | 540 days |
| Jiang 2007(26)  \*Abstract  USA  Retrospective cohort | To compare adherence and wastage among 30-day retail program, mandatory 90-day retail program and voluntary 90-day retail program. | Patients who were new to ACE-inhibitor statins or SSRIs | Not explicitly reported; pharmacy claims data (Walgreens) | * Anti-depressants (SSRIs) * Anti-hypertensives (ACE inhibitors) * Lipid lowering agents (statins) | 90-day supply, either mandatory or voluntarily, compared to 30-day supply | 1,685 | * Adherence * Wastage | 1 year |
| Murphy 2012(29)  USA  Retrospective cohort | To examine medication wastage for patients filling 90-day supplies of medication compared with those filling 30-day prescriptions. | Adults with repeat prescriptions for ongoing care | Not explicitly reported; pharmacy claims data (Walgreens) | * Anti-depressants (SSRIs; Tricyclics) * Diabetic medications (biguanides; insulin) * Anti-hypertensives (Alpha-beta blockers; ACE inhibitors; Angiotensin II receptor antagonists; calcium channel blockers; cardioselective beta-blockers; Loop diuretics; Thiazides) * Lipid lowering agents (statins; fibric acid derivatives) * Thyroid hormones | 90-day supply compared to 30-day supply  90 day supply stratified in two prescription fulfilment groups: mail and retail | 60,358 | * Wastage | 1 year |
| Pfeiffer 2012(30)  USA  Retrospective cohort | To examine whether receipt of an initial 90-day supply of an antidepressant was associated with better or worse longer-term antidepressant coverage compared with patients who initially received less than a 90-day supply. | Adult patients newly diagnosed with major depression | Not explicitly reported; pharmacy claims from  Veterans Affairs National Registry for Depression.  Variety of settings including primary care, mental health clinics and inpatient services | * Anti-depressants | 90-day supply compared to less than 90-day supply | 383,634 | * Adherence * Other (clinical encounters) | 7 years |
| Ryvkin 2009(27)  \*Abstract  USA  Retrospective cohort | To quantify medication wastage for Lipid Lowering Agents, Antihypertensive Therapy and Proton Pump Inhibitors. | Patients new to therapy | Not explicitly reported; pharmacy claims data (Medco Health Solutions) | * Anti-hypertensives * Lipid-lowering agents * Anti-ulcers (Proton pump inhibitors) | 30 to 90-day supply and more than 90-day supply compared to 30-day supply | 43,318 | * Wastage | Not reported |
| Schectman 2002(33)  USA  Cross-sectional  study | To evaluate the association between multiple demographic and prescription factors with the adherence behaviour of an indigent rural population to determine whether such factors could assist in targeting interventions. | Low-income patients without prescription insurance coverage, on hypertension, hypercholesterolemia or oral diabetes medication. | Academic internal medicine practice | 42 medications:   * Anti-hypertensives * Diabetic medication * Lipid lowering agents | n/a looking at factors associated with adherence among a population receiving standard care.  Prescription length varied, maximum supply was 90 days. | 1,984 | * Adherence | 9 months |
| Schmittdiel 2015(34)  USA  Cross-sectional  study | To examine the relationship between Medicare STAR medication adherence metrics and modifiable health system-level characteristics in a cohort of Medicare-aged diabetes patients | Adults aged 65 years and older with diabetes | Not explicitly reported; electronic health data from the three largest Kaiser Permanente health care delivery sites | * Anti-hypertensives (ACE inhibitors; angiotensin II receptor blockers) * Diabetic medications (oral anti-hyperglycemics) * Lipid lowering agents (statins) | n/a looking at four health-system level factors associated with adherence. Days' supply was derived from pharmacy electronic medication dispensing records. Categorised as: less than 30-day, 31 to 60-day, 61 to 90-day and more than 90-day supply. | 236,025 | * Adherence | Up to 1 year |
| Steiner 1993(31)  USA  Retrospective cohort | To determine whether large prescriptions (≥90 days' supplies) enhance the acquisition of maintenance medications by patients. | Patients who had received digoxin prescriptions in the previous year (ongoing care) | Not explicitly reported; pharmacy records from ten Veteran Affairs Medical centres | * Digoxin | 31 to 89-day supply and more than 90-day supply compared to 30-day supply | 120 | * Adherence | 14 months |
| Taitel 2012(32)  USA  Retrospective cohort with a cost consequence analysis | To determine whether 90-day refills at community pharmacies could improve adherence, minimise wastage and control costs. | Medicaid patients | Not explicitly reported; pharmacy claims data (Walgreens) | * Anti-depressants (SSRIs) * Diabetic medications (oral hypoglycemics) * Anti-hypertensives * Lipid lowering agents (statins) | 90 day prescription (day supply greater than or equal to 84 days) compared to 30 day prescription (day supply less than 84 days) | 52,898 | * Adherence * Cost * Wastage * Other (persistency) | 1 year |
| Walton 2001(35)  USA  Cross-sectional study and cost analysis | To investigate the relative roles that fill quantity, dispensing costs, and wasted medication play in the total cost of outpatient prescriptions | Outpatients receiving ongoing care and new to treatment through Veteran Administration's Chicago Health Care System | Outpatient prescription data from the Veteran Administration's Chicago Health Care System | * Lipid lowering agents (statins) | 90-day supply compared to 30-day supply | 16,990 prescriptions | * Cost * Wastage | 1 year |

# Appendix 4: Studies that evaluated medication adherence

| **Reference, study type** | **Condition(s)/**  **Medication(s) evaluated** | **Adherence measurement (as reported by the study authors)** | **Duration of study** | **90-days’ supply (unless otherwise stated)** | **30-days’ supply (unless otherwise stated)** | **Effect size** |
| --- | --- | --- | --- | --- | --- | --- |
| **Dichotomous outcomes (≥80% adherence)** | | | | | | |
| Batal 2007(28)  Retrospective cohort | * Lipid lowering agents (statins) | Pharmacy refills; each patient’s adherence score was calculated as their days of drug acquired divided by their days in the study (days from first prescription fill to last prescription fill). Primary outcome was proportion with ≥ 80% adherence. | 3 years | **60-day supply:**  1307/2553 (51%) | 303/833 (36%) | OR 0.53 (95% CI: 0.45, 0.62)1 |
| Domino 2011(36)  Before and after controlled study with a cost consequence analysis | * Anti-depressants * Anti-psychotics * Anti- hypertensives * Diabetic medications * Seizure disorder medications * Lipid lowering agents (statins) | Proportion of days covered (PDC) measure; calculates daily indicators of medication used divided by the number of days in the quarter. The outcome was reported as difference-in-difference-in-differences2 in the percent of quarters in which individuals had PDC ≥ 80% | 18 months | NR | NR | Statins: -0.132 (0.025), p<0.01  Diabetes: -0.053 (0.017), p<0.01  Antihypertensives: -0.083 (0.006), p<0.01  Seizure disorder: -0.022 (0.014), p=ns  Antidepressants: -0.027 (0.021), p=ns  Antipsychotics 0.004 (0.018), p=ns |
| Hermes 2010(25)  \*Abstract  Retrospective cohort | * Anti-hypertensives * Diabetic medications * Cholesterol lowering agents | Proportion of days covered (PDC) (no further details reported). Primary outcome was the proportion with a PDC ≥ 80%. | 540 days | Cholesterol lowering: 5,4143/ 7,219 (74.9%)  Anti- hypertensives: 7,928/ 9,405 (84.3%)  Diabetic medications: 1,221/ 1,578 (77.4%) | Cholesterol-lowering: 20,820/ 31,982 (65.1%)  Anti - hypertensives: 41,064/ 53,192 (77.2%)  Diabetic medications: 6,094/ 8,844 (68.9%) | Cholesterol-lowering:4 OR 0.62 (95% CI: 0.59, 0.66)  Anti-hypertensives: OR 0.63 (95% CI: 0.59, 0.67)  Diabetic medications: OR 0.65 (95% CI: 0.57, 0.74) |
| Pfeiffer 2012(30)  Retrospective cohort | * Anti-depressants | Proportion of patients who received at least 180 days of an antidepressant treatment out of the 231-day period following the index prescription. The primary outcome was the proportion with >80% adherence. | 7 years | 67,0775/ 87,000 (77.1%) | ‘Less than a 90 day supply’:  123,993/ 296,634 (41.8%) | OR 0.21 (95% CI: 0.21, 0.22) |
| Schmittdiel 2015(34)  Cross-sectional study | * Anti-hypertensives (ACE inhibitors; angiotensin II receptor blockers) * Diabetic medications (oral anti-hyperglycemics) * Lipid lowering agents (statins) | Proportion of Days Covered (PDC); the percent of days in the measurement period "covered" by prescription fills for the same medication or medications in the same therapeutic category. Primary outcome was predictors of adherence modelled as a dichotomous outcome in a Poisson regression model. | Up to 1 year | NR | NR | Estimated RR of being adherent (PDC ≥0.8) (reference group with <31 days’ supply):6  ACEI/ARB: 61-90 days 1.35; >90 days 1.61  Oral diabetes medications: 61-90 days 1.48; >90 days 1.61  Statins: 61-90 days 1.47; >90 days 1.61 (p<0.001 for all) |
| **Continuous (mean PDC or MPR)** | | | | | | |
| Domino 2011(36)  \*Same as above  Before and after controlled study with a cost consequence analysis | * Anti-depressants * Anti-psychotics * Anti- hypertensives * Diabetic medications * Seizure disorder medications * Lipid lowering agents (statins) | Proportion of days covered (PDC) measure; as above. | 18 months | NR | NR | Statins: -0.080 (0.012), p<0.01  Diabetes: -0.034 (0.008), p<0.01  Antihypertensives: -0.045 (0.002), p<0.01  Seizure disorder: -0.009 (0.006), p=ns  Antidepressants: -0.030 (0.010), p<0.01  Antipsychotics: -0.010 (0.008), p=ns |
| Jiang 2007(26)  \*Abstract  Retrospective cohort | * Anti-depressants (SSRIs) * Anti-hypertensives (ACE inhibitors) * Lipid lowering agents (statins) | Medication Possession Ratio (MPR) (no further details reported) | 1 year | Mandatory 90-days:  0.7543 (SD not reported)7 (n=148)  Voluntary 90-days:  0.6895 (SD not reported) (n=582) | 0.3999 (SD not reported) (n=955) | MD -0.30 (95% CI:-0.58, -0.03)8 |
| Schectman 2002(33)  Cross-sectional study | 42 medications:   * Anti-hypertensives * Diabetic medications * Lipid lowering agents | Number of days of therapy dispensed between first and last refill, divided by interval between first and last refill. Primary outcome was predictors of adherence modelled in a multivariable linear regression model. No details on whether or not MPR was capped at 100%. | 9 months | NR | NR | Based on multivariate analysis, each 30-day increment in prescription drug supply (maximum supply was 90 days) was associated with a 5.7% increase in mean adherence (p<0.0001)9 |
| Steiner 1993(31)  Retrospective cohort | * Digoxin | The proportion of prescribed dose of maintenance medication obtained. Calculated as the total days' supply divided by the number of days between the first and last fills. | 14 months | 31 to 89 days:  103.6%\* (SD 26.6) (n=41)  ≥ 90 days:  113.0%\* (SD 21.4) (n=46) \*presented as rate in the forest plot | 89.7% (SD 34.9) (n=27) | ≥ 90 days vs. ≤30 days: MD -0.23 (95% CI: -0.38, -0.09) |
| Taitel 2012(32)  Retrospective cohort with a cost consequence analysis | * Anti-depressants (SSRIs) * Diabetic medications (oral hypoglycemics) * Anti-hypertensives * Lipid lowering agents (statins) | Medication possession ratio (MPR); sum of the days’ supply for each therapeutic area divided by 365, the number of days in the follow-up period. | 1 year | Anti-hypertensives: 0.910 (SD 0.174)10 (n=5,835)  Statins: 0.819 (SD 0.194) (n=2,162)  SSRIs: 0.817 (SD 0.196) (n=266)  Hypoglycemics: 0.875 (SD 0.190) (n=1,511) | Anti-hypertensives: 0.774 (SD 0.292) (n= 33,009)  Statins: 0.671 (SD 0.278) (n=12,136)  SSRIs: 0.611 (SD 0.295) (n=7,017)  Hypoglycemics: 0.775 (SD 0.289) (n=11,842) | Anti-hypertensives: MD -0.14 (95% CI: -0.14, -0.13)  Statins: MD -0.15 (95% CI: -0.16, -0.14)  SSRIs: MD -0.21 (95% CI: -0.23, -0.18)  Hypoglycemics: MD -0.12 (95% CI: -0.13, -0.11) |

Notes: MD = mean difference, NR = not reported, OR = Odd Ration, RR = Risk Ratio,

1The authors reported an adjusted RR 1.41 (95% CI: 1.28 to 1.55), p<0.01, controlling for age, gender, race, co-payment, comorbidities, and insurance status; Given that this is a retrospective cohort study, we have presented the effect size as an odds ratio;

2 Differences-in-differences-in-differences measures = differences from baseline to follow-up between two states (North Carolina and Georgia);

3 Numerators were calculated from data presented in the abstract;

4 The authors reported the following effect sizes: Cholesterol OR 0.60 (95% CI: 0.57 to 0.64), p<0.001; Hypertension OR 0.60 (0.56 to 0.63), p<0.001; Diabetes OR 0.61 (95%CI 0.53 to 0.70), p<0.001. Our calculated ORs, as presented in the forest plot and table, are similar;

5 Numerators were calculated from data presented in the text;

6 Regression models adjusted for site and whether patient was enrolled in health plan;

7 The authors were contacted, but SDs were not available;

8 We combined the means from the mandatory and voluntary 90 days groups. Standard deviations were imputed in order to calculate an effect size (based on p<0.01);

9 In the multivariate model for mean adherence, each day supply had a parameter estimate of 0.19, so that for 30 days, adherence was estimated to be 5.7%;

10 Means and SDs were obtained from the study authors.

# Appendix 5: Studies that evaluated medication wastage

| **Reference, study type** | **Condition(s)/**  **Medication(s) evaluated** | **Wastage definition and calculation (as reported by the study authors)** | **Duration of study** | **90-days’ supply (unless otherwise stated)** | **30-days’ supply (unless otherwise stated)** | **Effect size** |
| --- | --- | --- | --- | --- | --- | --- |
| **Percentage of days’ supply wasted** | | | | | |  |
| Faris 2010(24)  \*Abstract  Retrospective cohort | Medications for:   * Multiple sclerosis * Rheumatoid arthritis * Oncology * Growth hormone | Wastage occurred when patients switched medication or stopped taking therapy (drop off waste). Outcome measured: proportion of days’ supply wasted calculated as the sum of switch waste and drop off waste, divided by total days supplied. | 21 months | Multiple sclerosis: 2.44%  Rheumatoid arthritis: 2.73%  Oncology: 1.90%  Growth hormone: 4.28%  (sample sizes and SDs were not reported) | Multiple sclerosis: 2.55%  Rheumatoid arthritis: 3.97%  Oncology: 3.42%  Growth hormone: 3.54%  (sample sizes and SDs were not reported) | An effect size was not reported and could not be calculated |
| Ryvkin 2009(27)  \*Abstract  Retrospective cohort | * Anti-hypertensives * Lipid-lowering agents * Anti-ulcers (Proton pump inhibitors) | Defined as a switch within therapeutic area. Outcome measured: proportion of days’ supply wasted. | Not reported | Anti-hypertensives:  2.0% (sample sizes and SDs not reported)  Lipid-lowering agents:  1.2% (sample sizes and SDs not reported)  Proton pump inhibitors:  0.7% (sample sizes and SDs not reported) | Anti-hypertensives:  2.1% (sample sizes and SDs not reported)  Lipid-lowering agents:  0.4% (sample sizes and SDs not reported)  Proton pump inhibitors:  0.7% days (sample sizes and SDs not reported) | An effect size was not reported and could not be calculated |
| **Mean number of days’ supply wasted** | | | | | | |
| Jiang 2007(26)  \*Abstract  Retrospective cohort | * Anti-depressants (SSRIs) * Anti-hypertensives (ACE inhibitors) * Lipid lowering agents (statins) | Wastage occurred either when patients switched to different medication within the same therapeutic area or to similar medication having different strength and that the patients' actual days' supply was less than the dispensed days' supply. Outcome measured: total days' supply wasted among a normalised 30-day period. | 1 year | All therapeutic areas:  Mandatory 90 days: 2.5 days per 30-day period (n=148)  Voluntary 90 days: 2.2 days per 30-day period (n=582) | All therapeutic areas:  2.3 days per 30-day period (n=955) | MD -0.10 (95% CI: -0.20, -0.00)1 |
| Murphy 2012(29)  Retrospective cohort | * Anti-depressants (SSRIs; Tricyclics) * Diabetic medications (biguanides; insulin) * Anti-hypertensives (Alpha-beta blockers; ACE inhibitors; Angiotensin II receptor antagonists; calcium channel blockers; cardioselective beta-blockers; Loop diuretics; Thiazides) * Lipid lowering agents (HMG CoA reductase inhibitors; Fibric acid derivatives) * Thyroid hormones | Wastage was defined as an excess days’ supply of medication resulting from a switch in medication within the same therapeutic areaor to the same medication but different strength occurring before the expected refill date. Outcome measured: mean number of days wasted calculated as the sum of the excess days divided by the total number of fills which were converted to 30-day equivalents. | 1 year | Anti-depressants:  SSRIs: 0.142 days per 30-day period (SDs not reported) (n=3,337)  Tricyclics: 0.147 days per 30-day period (n=456)  Diabetic medications:  Insulins: 0.512 days per 30-day period (n=546)  Biguanides: 0.131 days per 30-day period (n=1938)  Anti-hypertensives:  Cardioselective beta-blockers: 0.144 days per 30-day period (n=4,353)  Alpha beta-blockers: 0.202 days per 30-day period (n=554)  Calcium channel blockers: 0.156 days per 30-day period (n=3,246)  ACE inhibitors: 0.134 days per 30-day period (n=4,786)  Angiotensin II receptor antagonists: 0.247 days per 30-day period (n=2,224)  Loop diuretics: 0.100 days per 30-day period (n=556)  Thiazides: 0.062 days per 30-day period (n=1,778)  Lipid lowering agents:  HMG CoA reductase inhibitors: 0.118 days per 30-day period (n=10,674)  Fibric acid derivatives: 0.079 days per 30-day period (n=1,236)  Thyroid hormones: 0.383 days per 30-day period (n=4,846) | Anti-depressants:  SSRIs: 0.157 days per 30-day period (SDs not reported) (n=7,969)  Tricyclics: 0.131 days per 30-day period (n=1,091)  Diabetic medications:  Insulins: 0.281 days per 30-day period (n=1,545)  Biguanides: 0.082 days per 30-day period (n=3,429)  Anti-hypertensives:  Cardioselective beta-blockers: 0.087 days per 30-day period (n=5,458)  Alpha beta-blockers: 0.114 days per 30-day period (n=934)  Calcium channel blockers: 0.127 days per 30-day period (n=4,249)  ACE inhibitors: 0.102 days per 30-day period (n=6,371)  Angiotensin II receptor antagonists: 0.117 days per 30-day period (n=2,451)  Loop diuretics: 0.151 days per 30-day period (n=1,179)  Thiazides: 0.024 days per 30-day period (n=2,335)  Lipid lowering agents:  HMG CoA reductase inhibitors: 0.086 days per 30-day period (n=10,410)  Fibric acid derivatives: 0.079 days per 30-day period (n=1,710)  Thyroid hormones: 0.252 days per 30-day period (n=6,725) | Anti-depressants:  SSRIS: MD 0.02 (95% CI: -0.03, 0.06)2  Tricyclics: MD -0.02 (95% CI: -0.06, 0.03)  Diabetic medications:  Insulins: MD -0.23 (95% CI: -0.43, -0.04)  Biguanides:  MD -0.02 (95% CI: -0.06, 0.03)  Anti-hypertensives:  Cardioselective beta-blockers: MD -0.06 (95% CI: -0.11, -0.01)  Alpha beta-blockers: MD -0.09 (95% CI: -0.20, 0.03)  Calcium channel blockers: MD -0.03 (95% CI: -0.08, 0.02)  ACE inhibitors: MD -0.03 (95% CI: -0.07, 0.00)  Angiotensin II receptor antagonists: MD -0.13 (95% CI: -0.24, -0.02)  Loop diuretics: MD 0.05 (95% CI: -0.06, 0.16)  Thiazides: MD -0.04 (95% CI: -0.07, -0.00)  Lipid lowering agents:  HMG CoA reductase inhibitors: MD -0.03 (95% CI: -0.06, 0.00)  Fibric acid derivatives: MD 0.0 (95% CI: 0.00, 0.00)  Thyroid hormones: MD -0.13 (95% CI: -0.24, -0.02) |
| Taitel 2012(32)  Retrospective cohort with a cost consequence analysis | * Anti-depressants (SSRIs) * Diabetic medications (oral hypoglycemics) * Anti-hypertensives * Lipid lowering agents (statins) | Defined as a switch of drug type or strength within the same therapeutic area that occurred before the expected refill date. Outcome measured: average number of waste days. | 1 year | Antihypertensives:  9.211 days (SD 30.284)3 (n=5,835)  Statins:  5.757 days (SD 22.205) (n=2,162)  SSRIs:  10.425 days (SD 32.463) (n=266)  Hypoglycemics:  7.899 days (SD 25.385) (n=1,511) | Antihypertensives:  4.037 days (SD 16.236) (n= 33,009)  Statins:  2.251 days (SD 10.673) (n=12,136)  SSRIs:  3.501 days (SD 12.941) (n=7,017)  Hypoglycemics:  3.289 days (SD 13.441) (n=11,842) | Antihypertensives:  MD -5.17 (95% CI: -5.97, -4.38)  Statins:  MD -3.51 (95% CI: -4.46, -2.55)  SSRIs:  MD -6.92 (95% CI: -10.84, -3.01)  Hypoglycemics:  MD -4.61 (95% CI: -5.91, -3.31) |
| Walton 2001(35)  Cross-sectional study | * Lipid lowering agents (HMG CoA reductase inhibitors) | Defined as a switch within therapeutic area. Outcome measured: mean number of days wasted calculated as the difference between the average quantity dispensed and the average quantity used for each group. If a switch occurred, the quantity used was calculated as the difference between the date the first prescription was dispensed and the date the second, different prescription was dispensed. | 1 year | 5.33 days (SD not reported) (n=3,635) | 1.06 days (SD not reported) ‘for each 30-day fill period’ (n=13.355) | An effect size was not reported and could not be calculated.  It is not clear if these results are standardised for the same time period and therefore if the results are comparable. |
| **Proportion of patients that wasted medication** | | | | | |  |
| Ryvkin 2009(27)  \*Abstract  Retrospective  cohort | * Anti-hypertensives * Lipid-lowering agents * Anti-ulcers (Proton pump inhibitors)1 | Defined as a switch within therapeutic area. Outcome measured proportion of patients that wasted medication. | Not reported | Anti-hypertensives:  5.2% (sample sizes not reported)  Lipid-lowering agents:  2.9% (sample sizes not reported)  Proton pump inhibitors:  1.8% (sample sizes not reported) | Anti-hypertensives:  6.3% (sample sizes not reported)  Lipid-lowering agents:  1.2% (sample sizes not reported)  Proton pump inhibitors:  1.9% (sample sizes not reported) | An effect size was not reported and could not be calculated |
| Taitel 2012(32)  Retrospective cohort with a cost consequence analysis | * Anti-depressants (SSRIs) * Diabetic medications (oral hypoglycemics) * Anti-hypertensives * Lipid lowering agents (statins) | Defined as a switch of drug type or strength within the same therapeutic area that occurred before the expected refill date. Outcome measured: percentage of patients that wasted medication. | 1 year | Anti-hypertensives:  7124/5,835 (12.2%)  Statins:  212/2,162 (9.8%)  SSRIs:  39/266 (14.7%)  Hypoglycemics:  175/1,511 (11.6%) | Anti-hypertensives:  3,928/33,009 (11.9%)  Statins:  1,104/12,136 (9.1%)  SSRIs:  975/7,017 (13.9%)  Hypoglycemics:  1,255/11,842 (10.6%) | Anti-hypertensives:  OR 0.97 (95% CI: 0.89, 1.06)  Statins:  OR 0.84 (95% CI: 0.72, 0.98)  SSRIs:  OR 0.94 (95% CI: 0.66 1.33)  Hypoglycemics:  OR 0.90 (95% CI: 0.76, 1.07) |
| Walton 2001(35)  Cross-sectional study | * Lipid lowering agents (HMG CoA reductase inhibitors) | Defined as a switch within therapeutic area. Outcome measured: proportion of patients that switched. | 1 year | 545/3,635 (15.0%) | 1,909/13,355 (14.3%) | OR 0.95 (95% CI: 0.85, 1.05) |

Notes: MD = mean difference, OR = odds ratio, SD = standard deviation

1 We combined the means from the mandatory and voluntary 90 day groups. Standard deviations were imputed in order to calculate an effect size (based on p>0.05);

2 Standard deviations were imputed in order to calculate an effect size (p values were reported for each comparison).

3 Means and SDs were obtained from the study authors;

4 Numerators have been calculated based on overall sample sizes and percentages.

# Appendix 6: Risk of bias assessment

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Bias due to confounding** | **Bias in selection of participants into the study** | **Bias in classification of interventions** | **Bias due to departures from intended interventions** | **Bias due to missing data** | **Bias in measurement of outcomes** | **Bias in selection of the reported result** | **Overall bias** |
| Batal 2007 | Low | Moderate | Low | Low | Low | Low | Low | **Moderate** |
| Domino 2011 | Low | Low | Low | Moderate | Moderate | Low | Low | **Moderate** |
| Faris 2010\* | No information | No information | Low | No information | No information | Low | No information | **No information** |
| Hermes 2010\* | Moderate | Moderate | Low | No information | No information | Low | No information | **No information** |
| Jiang 2007\* | No information | Moderate | Low | No information | No information | Low | No information | **No information** |
| Murphy 2012 | Low | Moderate | Low | Low | Moderate | Low | Low | **Moderate** |
| Pfeiffer 2012 | Low | Moderate | Low | Low | Low | Low | Low | **Moderate** |
| Ryvkin 2009\* | No information | No information | Low | No information | No information | Low | No information | **No information** |
| Schectman 2002 | Moderate | No information | No information | Moderate | No information | Low | Low | **Moderate** |
| Schmittdiel 2015 | Low | Moderate | Low | Moderate | Low | Low | Low | **Moderate** |
| Steiner 1993 | Serious | Moderate | Low | Low | No information | Low | Low | **Serious** |
| Taitel 2012 | Moderate/Serious | Moderate | Serious | Moderate | Low | Low | Low | **Serious** |
| Walton 2001 | Moderate/Serious | Moderate/Serious | Low | Low | Low | Low | Low | **Moderate** |

\* *reported as abstract only*