

# Clinical and cost-effectiveness of issuing longer versus shorter duration (3 month vs. 28 day) prescriptions for prescribed medication in patients with stable, chronic conditions

## A systematic review protocol

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## Abbreviations

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GP	General Practitioners
NICE	National Institute for Health and Care Excellence
RCT	Randomised Controlled Trial
SR	Systematic Review

# 1. Introduction

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## 1.1. Summary of proposed project

The systematic review described in this protocol will be part of a larger project commissioned by the NIHR Health Technology Assessment Programme that will evaluate quantitative, qualitative, and cost evidence surrounding prescription length, particularly in patients with chronic stable disease. The review will be followed by economic modelling, which is not described in this protocol. RAND Europe, in collaboration with researchers from the Universities of Cambridge and Nottingham will complete the project work.

## 1.2. Background

In an effort to reduce expenditure on, and wastage of, drugs some commissioners have encouraged General Practitioners (GPs) to issue shorter prescriptions, typically 28 days in length.[1 2] This move towards shorter prescription lengths reflects the Department of Health's policy on prescribing, which advocates a 28-day repeat prescribing interval.[2] The Department of Health's reported rationale for advocating prescription intervals of 28 days was to strike a balance between patient convenience, good medical practice and drug wastage. However, overall, the DH's view is that prescription intervals should be consistent with medically appropriate patient needs while also considering NHS resources, patient convenience and the dangers of having excess quantities of prescription medications in the home.[3]

The waste of prescription drugs is of great importance to the healthcare system. The NHS spends approximately £8 billion on prescriptions dispensed in the community per year, of which it has been estimated that £100m to £300m was wasted in 2007 and 2009 [4]. There is some evidence to suggest that limiting prescription length to 28 days reduces medicine waste.[5] A 1996 study estimated that the returns of unused drugs to pharmacies could have been reduced by a third if prescriptions were limited to 28 days [5] (£50m in 2009 prices [4]). In another study, 13% and 16% reductions in drug costs were observed following the introduction of 28-day prescriptions in East Surrey and Grampian.[6]

Shorter prescriptions, however, may increase the costs to the health system through increased GP workload and dispensing fees to pharmacists (supply side costs).[4] Recent evidence suggested that dispensing fees, as a result of increased numbers of shorter prescriptions, cost the NHS approximately £150 million in 2009.[7] If all 842.5m prescription items dispensed in the community in England in 2008 had been 28-day repeats, dispensing fees would have been 50% higher (£700m increase on £1.5bn current

expenditure).[8] This same conclusion followed from a simulation model published in 2004 comparing 100-day with 34-day supplies in a US Medicaid setting:[9] shorter prescription lengths were associated with a reduction in drug wastage of 5-14%. However, increases in dispensing fees more than exceeded this decrease in drug wastage. Shorter prescriptions may also incur costs to the patient, e.g. at £8.20 per item, then 3 prescriptions per month would be £24.60 (although patients can get a prepayment certification if they have more than a certain number of items, where they pay a flat fee<sup>1</sup>). The authors of the above study noted that shorter prescriptions increased burden on patients through increased transportation costs and other expenses.[9]

Prescription duration may also have a direct impact on patient satisfaction. For example, a survey of 2551 patients prescribed levothyroxine in 2007 found that 38% were given 28-day prescriptions. Of those, 59% reported being dissatisfied with 28-day prescriptions.[10] The authors of the survey concluded that despite reductions in drug wastage, given patient dissatisfaction, 28-day prescriptions were unlikely to be an “economically effective public health policy.” Similarly, a recent qualitative study of patient and carer experience of regular prescribed medication for chronic diseases in the NHS, found that participants most frequently described the process for ordering and obtaining regular medication as a recurring hassle.[7] The issues they raised included: multiple trips to the surgery and pharmacy, lack of synchronisation and dissatisfaction with the prescription duration.

Shorter prescription length, however, may provide better signalling to GPs for treatment discontinuations due to adverse events.[11] Poor adherence is associated with poorer control of chronic disease[12] with consequent increased risk of long term complications. Patient adherence to medication may, however, be due to a number of different factors and the impact of prescription duration on adherence is not entirely clear. A US-based study of predictors of adherence to repeat prescriptions for chronic diseases in a poor rural population found prescription length, together with age and race, to be associated with higher adherence, although these factors explained only a small proportion of overall variability in adherence.[13] For example, whilst longer prescription length was positively associated with adherence, this explained only 2% to 3% of total variation in adherence. This view is supported by a Cochrane review that found that almost all effective interventions aimed at increasing adherence were complex and comprised of factors such as more convenient care delivery, information, reminders, and self-monitoring.[14]

Given the disparity of the evidence, it is clear that a current review is needed to synthesise and assess the evidence on the effectiveness and cost-effectiveness of shorter versus longer duration prescriptions in terms of patients’ health outcomes and health system costs. Thus, this systematic review will synthesise both qualitative and quantitative evidence that evaluate the clinical and cost-effectiveness of longer versus shorter prescriptions. Specifically, the review will aim to assess the impact of different prescription lengths (e.g. 28-day vs. 3-month or longer) in patients with stable chronic conditions, on medication adherence and disease-specific health outcomes. Patients and members of the public will be involved directly in the research to help us identify outcomes that are of direct relevance to

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<sup>1</sup> Prepayment is currently £29.10 for 3 months and £104 for 12 month. This is only cheaper if more than one prescription is issued per month.

them. The review will assess all of the outcomes specified in the tender specifications, which include: adherence measures, disease specific measurements, drug wastage, adverse events, patient experience / satisfaction, professional administration time, pharmacist costs, health outcomes and cost-effectiveness. In addition to these outcomes, the review will also consider the following outcomes that were identified by our local public and patient involvement group, INsPIRE: patient time, patient costs and synchronisation of prescriptions (see Section 11 below for further details on our approach to PPI for this study).

The conclusions of this review will provide a comprehensive and transparent evidence base on whether shorter or longer repeat prescriptions have the largest impact on patient outcomes, and what prescription length would provide the best value for money – which would help inform health policy. In addition, this study will also be directly relevant to patient groups with stable, chronic conditions who require regular repeat prescriptions.

Thus, this review will aim to answer the following research question: What is the clinical and cost-effectiveness of issuing longer duration versus shorter duration (3 month versus 28 day) prescriptions for prescribed medication in patients with stable, chronic conditions requiring one or more repeat prescriptions in the primary care setting?

### 1.3. Objectives

The aim of this project is to provide a high quality reference on the clinical and cost-effectiveness of issuing longer duration versus shorter duration (3-month vs. 28-days) prescriptions in patients with stable chronic diseases. We will conduct a systematic review of the literature:

- (i) to assess whether shorter or longer prescription lengths have positive or negative impact on (defined) health outcomes, and patient experience – specifically in patients with chronic stable disease;
- (ii) to assess whether shorter or longer prescription lengths have an impact on patient adherence, wastage, GP time, dispensing costs, and costs to patients – in various patient groups<sup>2</sup>, including patients with chronic stable disease;
- (iii) to assess what previous published economic analyses there may be that evaluate the cost-effectiveness of different prescription lengths in patients with chronic stable disease.

Given the potential paucity of economic analyses, the systematic review will thus, also address the following questions in order to provide evidence with which to populate an economic model:

- What is the relationship between prescription length and drug wastage?

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<sup>2</sup> Not yet defined. We conducted a brief scoping review of the literature, and given the potential lack of evidence in the specific patient group of interest (i.e. patients with stable chronic disease), we will include other patient groups (not restricted at the searching stage). This is because the outcomes evaluated in this part of the systematic review will be used to inform the economic model.



- What is the relationship between prescription length and pharmacist dispensing fees and GP time?
- What is the relationship between prescription length and adherence to medication?

## 2. Methods

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### 2.1. Inclusion and exclusion criteria

To address the above research questions, the population(s), intervention(s), comparison(s), outcome(s), and study types of interest ('PICOS') are defined below and in Table 1.

#### *2.1.1. Populations*

Studies of patients being treated in a primary care setting with a stable chronic disease (including, but not limited to, hypothyroidism, diabetes, hypertension, cardiovascular disease, depression), requiring one or more repeat prescriptions will be eligible for inclusion. Studies of patients being treated in a primary care setting (with other [non-chronic] diseases, but requiring repeat prescriptions) may be included if the studies also report on an outcome of interest (other than health outcomes and patient experience). Patients in low-income countries or secondary/tertiary care outpatients will be excluded from this review.

#### *2.1.2. Interventions and comparisons*

This systematic review will focus on studies that specifically aim to evaluate the effects of prescription lengths, or compare two different prescription lengths. For this project, we are interested in 3- month prescriptions – or prescription lengths that span approximately two to four months, in comparison to 28-day prescriptions (or prescriptions around one month). The prescriptions may be for pharmaceutical medication, but may also include other medical prescriptions such as urostomy bags. Studies will be excluded if they evaluate excessively long prescription lengths (i.e. 12 months); studies will also be excluded if they evaluate prescriptions that do not require dispensing (e.g. physical activity prescriptions).

#### *2.1.3. Outcomes*

In studies of patients with or without chronic disease, the following outcomes are of interest:

- Adherence measures;
- Drug wastage;

- Adverse events (e.g. prescription error; drug monitoring error; adverse drug reaction; unplanned hospitalisation (including A&E attendance as well as admission for 'ambulatory care sensitive conditions; death);
- Professional administration time;
- Pharmacists' time/costs.

Additionally, in studies of patients with chronic disease only, the following outcomes are of interest:

- Health outcomes (any relevant health outcomes identified in the literature search will be included);
- Patient experience/satisfaction;
- Patient outcomes (any other relevant patient outcomes identified in the literature search will be included).

Economic outcomes of interest include all of the above as well as costs, quality adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs).

Studies will be excluded if they only report on prescribing patterns/trends, or if they evaluate the incidence of undertreatment or overtreatment of medicine, or if they report costs of generic vs branded prescribing. Studies that evaluate adverse events, without evaluating this outcome in direct association with prescription length, will also be excluded.

#### 2.1.4. Study designs

Systematic reviews, randomised controlled trials, observational studies, and economic evaluations will be eligible for inclusion. In addition, guideline and consensus statements will be summarised in a table for reference.

For the systematic review, studies published as abstracts or conference presentations will be included if enough data are presented, and if the abstract is not associated with a full paper.

For the economic review, published cost comparison studies and economic evaluations, such as cost-effectiveness analysis, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses, and cost-consequence analyses will be eligible for inclusion.

For the economic evaluation, studies published as abstracts or conference presentations will be included in the primary analysis provided that the costs and outcomes are sufficiently disaggregated.

Letters, editorials and commentaries will not be eligible for inclusion (unless new data are reported).

**Table 1. Summary of inclusion/exclusion criteria (this is same text as above)**

	Inclusion	Exclusion
Population	Studies of patients being treated in a primary care setting with a stable chronic disease (including, but not limited to, hypothyroidism, diabetes, hypertension, cardiovascular disease, depression), requiring one or more repeat	Patients in low-income countries; secondary/tertiary care outpatients.

	<p>prescriptions will be eligible for inclusion.</p> <p>Studies of patients being treated in a primary care setting (with other [non-chronic] diseases, but requiring repeat prescriptions) may be included if the studies also report on an outcome of interest (other than health outcomes and patient experience) – these patient groups will be defined at the protocol stage.</p>	
Intervention(s)	<p>Studies that specifically aim to evaluate the effects of prescription lengths, or compare two different prescription lengths will be eligible for inclusion. For this project, we are interested in 3- month prescriptions – or prescription lengths that span approximately two to four months. The prescriptions may be for pharmaceutical medication, but may also include other medical prescriptions such as urostomy bags.</p>	<p>Excessively long prescription lengths; prescriptions that do not require dispensing (e.g. physical activity prescriptions)</p>
Comparison(s)	<p>28-day (i.e. one month) prescription lengths (or prescriptions around one month)</p>	<p>Prescription lengths shorter than one month</p>
Outcome(s)	<p>In studies of patients with chronic disease only, the following outcomes are of interest:</p> <p>Health outcomes (any relevant health outcomes identified in the literature search will be included);</p> <p>Patient experience/satisfaction;</p> <p>Patient outcomes (any other relevant patient outcomes identified in the literature search will be included).</p> <p>In studies of patients <i>with or without</i> chronic disease, the following outcomes are of interest:</p> <p>Adherence measures;</p> <p>Drug wastage;</p> <p>Adverse events (e.g. prescription error; drug monitoring error; adverse drug reaction; unplanned hospitalisation (including A&amp;E attendance as well as admission for ‘ambulatory care sensitive conditions; death);</p> <p>Professional administration time;</p> <p>Pharmacists’ time/costs.</p> <p>Economic outcomes of interest include all of the above as well as costs, quality adjusted life years (QALYs),</p>	<p>Studies will be excluded if they only report on prescribing patterns/trends, or if they evaluate the incidence of undertreatment or overtreatment of medicine, or if they report costs of generic vs. branded prescribing. Studies that evaluate adverse events, without evaluating this outcome in direct association with prescription length, will also be excluded.</p>

	incremental cost-effectiveness ratios (ICERs).	
Studies design	<p>Systematic reviews, randomised controlled trials, observational studies, and economic evaluations will be eligible for inclusion. In addition, guideline and consensus statements will be summarised in a table for reference.</p> <p>For the systematic review, studies published as abstracts or conference presentations will be included if enough data are presented, and if the abstract is not associated with a full paper.</p> <p>For the economic review, published cost comparison studies and economic evaluations, such as cost-effectiveness analysis, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses, and cost-consequence analyses will be eligible for inclusion.</p> <p>For the economic evaluation, studies published as abstracts or conference presentations will be included in the primary analysis provided that the costs and outcomes are sufficiently disaggregated.</p>	<p>Letters, editorials and commentaries will not be eligible for inclusion (unless new data are reported).</p> <p>.</p>

## 2.2. Search Strategy

One search will be conducted to address both the clinical and cost effectiveness review questions. The literature search will be conducted in the following:

### **Databases:**

PubMed (NLM)

Embase (Elsevier) (includes conference proceedings)

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO)

Web of Science Core Collection\* (Thomson Reuters)

\* Science Citation Index, Citation Index – Science, Conference Proceedings Citation Index

Cochrane Library\* (Wiley)

\*includes: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of

Controlled Trials (CENTRAL), Database of Abstracts and Reviews (DARE), Health

Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED)

NIHR Health Technology Assessment (NIHR HTA and other NIHR journals)

NICE Technology appraisals

### **URLs (for grey literature):**

Oaister ([www.oaister.org](http://www.oaister.org))

OpenGrey ([www.opengrey.eu](http://www.opengrey.eu))

NYAM Grey Literature Report ([www.greylit.org](http://www.greylit.org))

## Search limits

No language or date restrictions will be imposed in the initial search stages.

## Additional searches

Additional techniques, typically used to identify evidence for systematic reviews will be applied:

- Checking the references within relevant papers and reviews;
- Searching for specific trial names;
- Carrying out citation searches of key publications to identify subsequent publications which have cited those key publications (e.g. we will check references of all included studies to make sure we haven't missed any potentially relevant studies in our searches).

All of the results of the searches will be loaded together into EndNote bibliographic software.

The search below is for the Medline search, and will be slightly adapted to fit the search syntax for each of the other databases.

**Table 2. Draft Search Terms**

"prescription lengths" [title/abstract] OR "prescription length"[title/abstract] OR "prescription duration"[title/abstract] OR "prescription durations"[title/abstract] OR "medication duration"[title/abstract] OR "medication durations"[title/abstract] OR "medication length"[title/abstract] OR "length of prescription"[title/abstract] OR "length of prescriptions"[title/abstract] OR "duration or 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 "prescribing patterns"[title/abstract] OR "prescription patterns"[title/abstract] OR "Prescription pattern"[title/abstract] OR "prescribing behavior"[title/abstract] OR "prescribing behaviour"[title/abstract] OR "prescribing behaviors"[title/abstract] OR "prescribing behaviours"[title/abstract] OR "prescribing practice"[title/abstract] OR "prescribing practices"[title/abstract] OR "prescribing standard"[title/abstract] OR "prescribing standards"[title/abstract] OR (installment[title/abstract] AND dispensing[title/abstract]) OR "repeat prescribing"[title/abstract] OR "repeat dispensing"[title/abstract] OR "repeat prescriptions"[title/abstract] OR "prescribing intervals"[title/abstract] OR "28 day supply"[Title/abstract] "30 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 "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 "dosage units"[title/abstract] OR "dosage unit"[title/abstract] OR ("unit dose"[title/abstract] AND supply"[title/abstract]) OR "prescription standardization"[title/abstract] OR "prescription standardisation"[title/abstract] OR "prescription restriction"[title/abstract] OR "prescription restrictions"[title/abstract] OR "prescribing restrictions"[title/abstract] OR "prescribing restriction"[title/abstract] OR "restricting prescriptions"[title/abstract] OR "restricting medication"[title/abstract] OR "medication restriction"[title/abstract] OR "medication restrictions"[title/abstract] OR "dispensing restrictions"[title/abstract] OR "dispensing restriction"[title/abstract] OR "prescribing trends"[title/abstract] OR "prescription trends"[title/abstract] OR "dispensing trends"[title/abstract] OR "trends in dispensing"[title/abstract] OR "trends in prescribing"[title/abstract] OR "prescription supply"[title/abstract] OR "prescription supplies"[title/abstract] OR "medication supply"[title/abstract] OR "medication supplies"[title/abstract] OR "long term prescription"[title/abstract] OR "long term prescriptions"[title/abstract] OR "short term prescription"[title/abstract] OR "short term prescriptions"[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 prescription"[title/abstract] OR "Standardised prescription"[title/abstract] OR "standardized prescriptions"[title/abstract] OR "Standardised prescriptions"[title/abstract] OR "standardized prescribing"[title/abstract] OR "Standardised prescribing"[title/abstract] OR "standardization of prescribing"[title/abstract] OR "standardisation of prescribing"[title/abstract] OR "standardization of prescriptions"[title/abstract] OR "standardisation of prescriptions"[title/abstract] OR "individualized prescribing"[title/abstract] OR "individualised prescribing"[title/abstract] OR "individualisation of prescribing"[title/abstract] OR "individualization of prescribing"[title/abstract] OR Drug Prescriptions/trends OR Drug Prescriptions/supply and distribution

### 2.3. Study selection and data extraction

Titles and abstracts of identified studies will be independently screened by two researchers for inclusion against the criteria specified in Table 1. This first screening phase will be conducted within Endnote – using the inclusion/exclusion criteria. A consensus will be drawn on the papers to be considered for full paper review, consulting a third reviewer if necessary.

During the next stage, full papers of potentially relevant studies identified in the first pass will be obtained and screened by two RAND researchers working independently, and using the inclusion criteria as a reference. Again, if there are any discrepancies, the opinion of a third reviewer will be sought.

The number of studies identified by the search and excluded at various stages will be recorded and reported in a PRISMA study flow diagram (see Appendix A). After the second

stage of screening, a table of excluded studies with detailed reasons for exclusion will be created and reported in an appendix in the final report.

An Excel spread sheet will be developed for data extraction and piloted using two or three studies. Data will be extracted twice by two reviewers working independently – so that two extraction forms will be created. The two forms will then be compared by another reviewer to find any discrepancies. If there are any discrepancies, these will be resolved through discussion or consultation with the team and the most senior reviewer. A third form will thus be created which is a 'clean' form (with all discrepancies resolved), and will be used as the Master document from which the results of the review are derived for analysis. This process minimises human error and ensures accurate reporting of the data. Data likely to be extracted from each study include:

- Bibliographic reference (authors, year, article title, journal, volume, pages);
- Study setting/country;
- Study type;
- Study quality;
- Key aims of the study (including the target audience);
- Study inclusion/exclusion criteria;
- Comparator evaluated;
- Method of allocation;
- Number of participants;
- Population characteristics (age, sex, ethnic origin; socio-economic status, education, other descriptive characteristics);
- The number of individuals recruited to the study (total, per treatment group);
- Prescription procedure evaluated;
- Methods of analysis;
- Results (including any adverse or unintended effects);
- Any factors the authors identified that may prevent, or support, effective implementation of the intervention evaluated;
- Comments (e.g. whether the intervention is transferable for other settings; limitations identified by authors and/or by reviewers).
- Gaps and limitations;
- Health outcomes and other patient outcomes (as noted above);
- Patient experience/satisfaction;
- Adherence measures;
- Drug wastage;
- Adverse events (as noted above);
- Professional administration time (e.g. GP/allied professional/nurse time);
- Pharmacists' time/costs.

Following identification of relevant economic studies, data will be extracted on:

- Analytic perspective of the study, setting and price year;
- Description of the interventions compared;
- Costs and resource use (including pharmacist's costs);
- Health outcomes, or valuation of health effects (HRQL);

- Incremental cost-effectiveness.

## 2.4. Quality assessment

To assess the quality of randomised controlled trials (RCTs), we will adapt questions from CRD 2009[16], and guidance developed by the Cochrane Collaboration:[17]

- Was randomisation carried out appropriately?
- Was the concealment of treatment allocation adequate?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

To determine the overall risk of bias of a study, we will use the guidance presented in the Cochrane Collaboration Handbook. For non-randomised trials, we will use or adapt different quality assessment tools (as per CRD guidance), such as the Newcastle-Ottawa scale.[18] The Newcastle-Ottawa quality assessment scale provides set criteria for evaluating case control studies and cohort studies. In particular, for case control studies, it looks at the sample selection, the comparability of cases and controls and the exposure of both. For cohort studies, it looks at sample selection, comparability and outcomes.

Economic evaluations will be summarised and quality assessed using the approaches suggested in NICE guidance (<http://publications.nice.org.uk/pmg6>), which are based on those of Drummond[19] and Philips[20]. Quality assessments will be conducted by two reviewers independently, with any discrepancies resolved through discussion or by consulting a third reviewer.

## 2.5. Synthesising the evidence

For qualitative studies, thematic analysis techniques will be used, and reported in a narrative synthesis. The approaches taken will largely follow those outlined by Noyes J and Lewin S (2011). As the review question aims to evaluate clinical effectiveness, we will primarily search for studies that specifically evaluate the effects of prescription lengths. Some of these intervention studies may report (partially or fully) qualitative outcomes, for example, data on patient experience/satisfaction. The results from these studies will be summarised narratively within themes, i.e. we will identify major/recurrent themes in the studies identified, and then summarise these findings under thematic headings. The results of any qualitative data will then be evaluated in parallel with the quantitative evidence.



It may also be the case that other types of qualitative evidence may be identified while looking for evidence of effectiveness, such as studies that report on barriers and facilitators to changing prescription lengths. While these types of studies are not currently included in the inclusion/exclusion criteria, they will be kept to one side, and may be briefly summarised in an appendix, depending on time and budgetary constraints. If included in the review, they could be used to supplement and extend the review.

For quantitative studies, meta-analysis will be undertaken (using the RevMan program) provided that there is no clinical or statistical heterogeneity<sup>3</sup> between studies. Where studies are sufficiently numerous and reasonably homogeneous, results will be pooled using a fixed effect model. Alternatively, if there is some heterogeneity among the studies a random-effects model will be used. Results will be presented as risk ratios for dichotomous outcomes and mean differences for studies that evaluate continuous outcomes (means, or mean differences), and presented in forest plots. For those studies that use different scales, a standardised mean will be estimated, and also presented in forest plots. If the data cannot be pooled, we will summarise the evidence in text and tables (i.e. using a narrative synthesis).

At this stage the main results will be summarised into general themes, and any qualitative studies will be presented alongside the quantitative analysis (i.e. in a parallel synthesis). Importantly, the degree of consistency across studies among the quantitative studies will also be considered, so that if all or most of the results are in a similar direction, one may be more confident in the pooled estimate of effect (if a meta-analysis can be conducted). Without knowing the consistency of the results between studies, it is impossible to determine the generalisability of the findings.

The clinical and cost-effectiveness evidence will then be synthesised to identify overall messages in consideration to study quality, and their relevance to the UK. We envision that the data will be presented by outcome evaluated, and within each outcome, by disease type and prescription duration. Thus, the results may be reported under the broader question headings such as:

- What is the relationship between prescription length and health outcomes, and also adverse events?
- What is the relationship between prescription length and patient experience/satisfaction?
- What is the relationship between prescription length and drug wastage?
- What is the relationship between prescription length and pharmacist dispensing fees and GP time?
- What is the relationship between prescription length and adherence to medication?

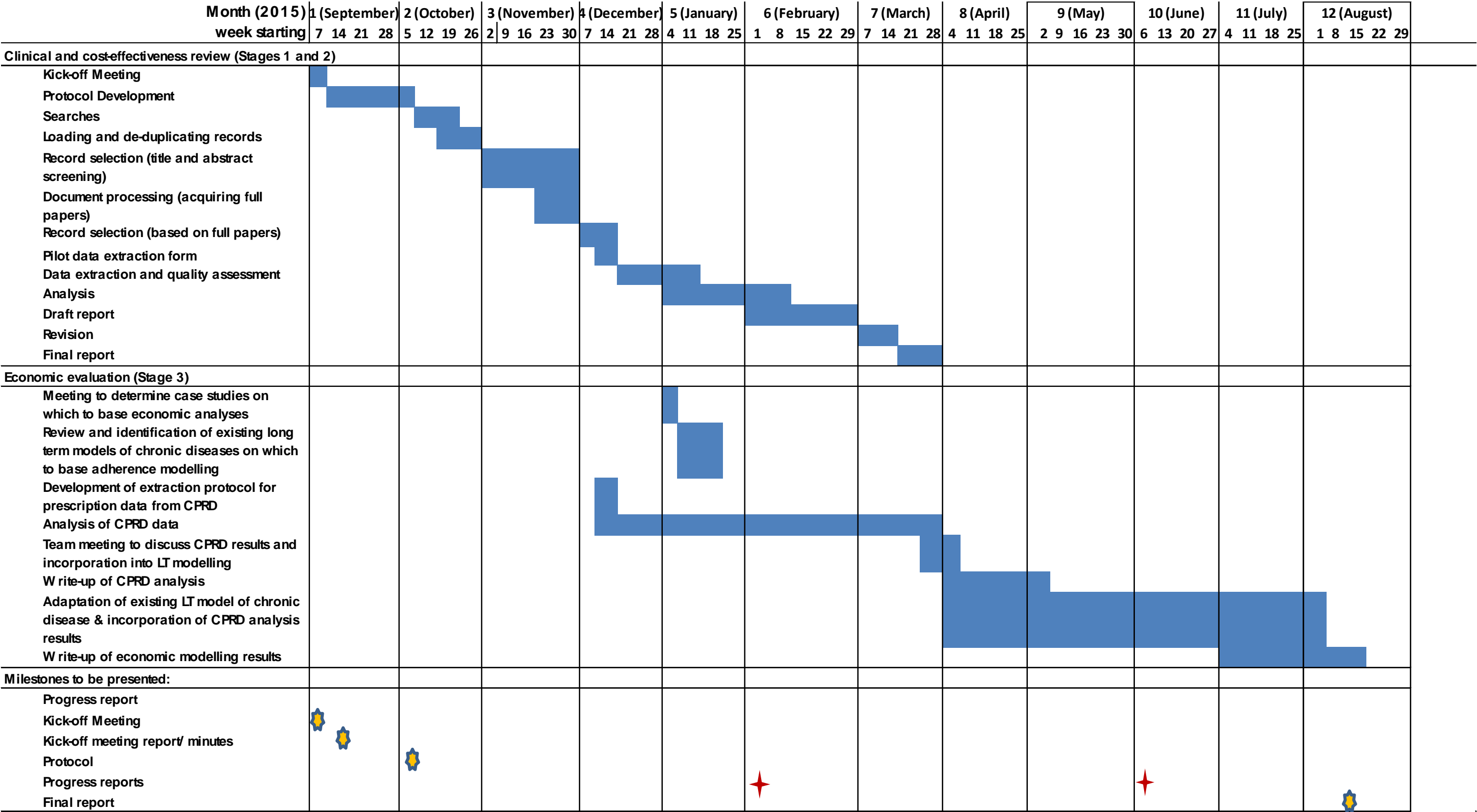
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<sup>3</sup> Consistency between study effect estimates is investigated using the Chi2 test (significance set at  $p < 0.1$ ) and the I2 statistic (with a value of  $\geq 50\%$ ). An I2 statistic  $< 25\%$  is considered to be a low level of heterogeneity, 25% to 50% a moderate level and  $> 50\%$  a high level. Subgroup analyses (i.e. grouping studies by factors such as age of participants or year of publication) may be conducted (specified a priori) to explore inconsistencies between study results that are unlikely to have arisen by chance alone. Sensitivity analyses may also be conducted (for example, omitting studies with lower quality from the analysis) to give an indication of the 'robustness' of the results.

- What are the costs of differing prescription lengths?

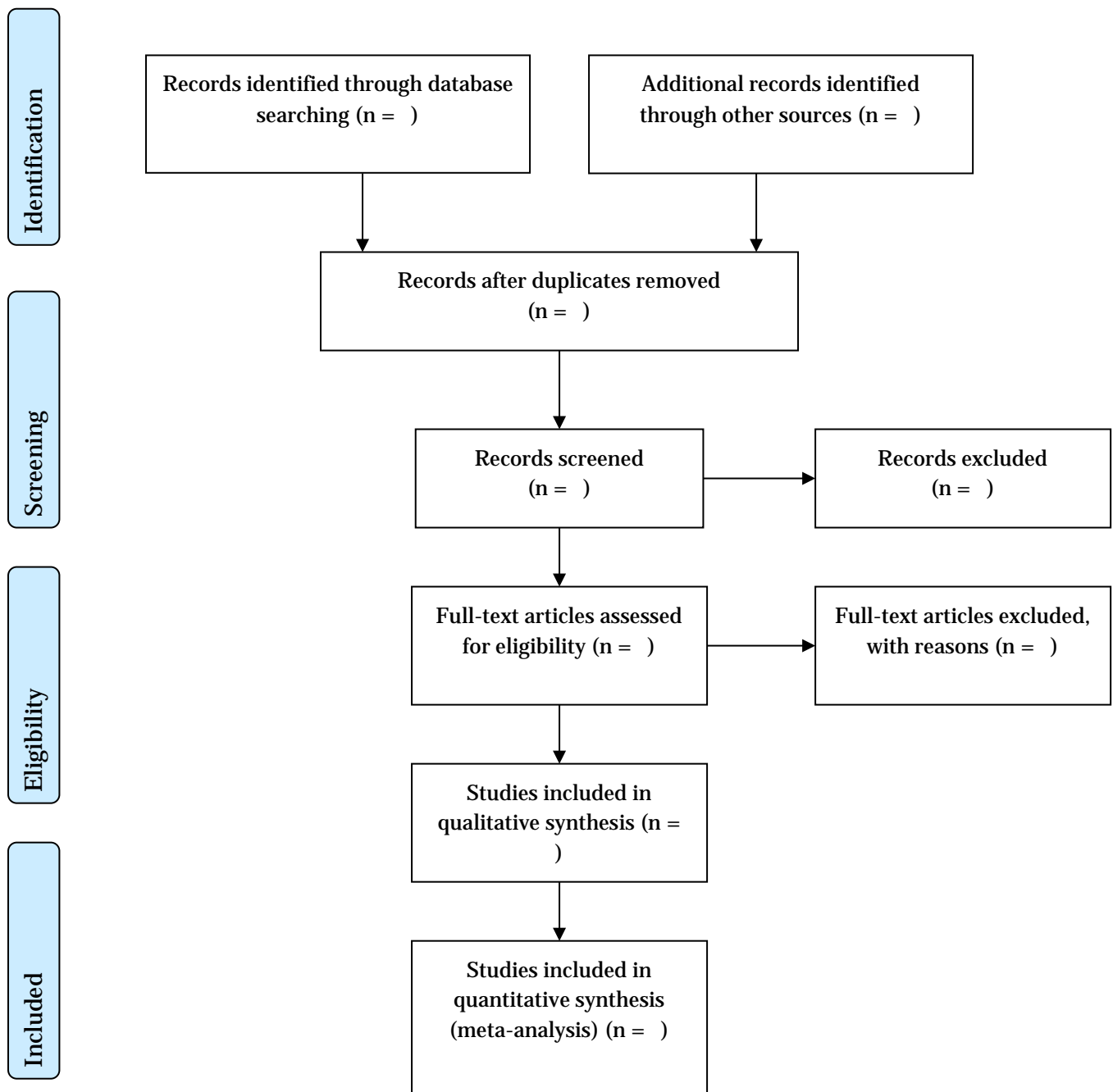
2.6. Timeline

Figure 1. Gantt chart



## Appendix A: PRISMA 2009 Flow Diagram

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