Assessing the Burden of Cardiovascular Disease through Medicines
- **ANALYSIS PLAN**

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Background:

Cardiovascular disease (CVD) remains the most common cause of mortality and morbidity in the UK despite advances in both prevention and acute treatments. The numbers of acute CVD events admitted to acute care settings during the first phase of the COVID-19 pandemic fell, which followed trends in other diseases as well as GP attendances. The indirect effects of COVID on CVD are yet to be fully experienced or measured. Some of these estimates may not be available for many years and it therefore may be difficult to judge in the short term what these impacts might be for individuals as well as the health economy.

What is even more intangible are the reduction in treatment of CVD risk factors which, when adequately controlled, reduce the burden of CVD events. For example, high blood pressure accounts for half of all myocardial infarctions (MI) and strokes; having atrial fibrillation (AF) makes it five times more likely that an individual will have a stroke; and in those with diabetes (when adequately diagnosed), CVD is the leading cause of morbidity and premature mortality.

Detection and treatment of risk factors has until now been through the Quality and Outcomes Framework (QOF), CVD health checks, and opportunistic screening most commonly in primary care. A Health Foundation analysis (using Clinical Practice Research Datalink, CPRD https://www.health.org.uk/news-and-comment/charts-and-infographics/use-of-primary-care-during-the-covid-19-pandemic) demonstrated that primary care visits fell an average of 30% from March-June 2020 with many of the existing visits being replaced by e- or telephone-consults. Primary care prescription pathways were also significantly affected, with repeat prescriptions spiking a week before the March lockdown and a reduction of new prescriptions following this.

Medicines are the method by which most conditions are treated and or prevented. This is particularly true of chronic, long term conditions like CVD where control of risk factors can have a significant impact. If CVD risk factors are not being adequately detected and/ or treated this will logically lead to higher burden of CVD in the future. Therefore, the reduction in new prescriptions for CVD risk factors could be used to model the impact of CVD risk burden to come.

In this proposal we seek to begin to estimate the changes in prescribing of drugs used for CVD and its major risk factors (high blood pressure, hyperlipidemia, atrial fibrillation, type II diabetes) at several time points prior to and during the COVID-19 pandemic to begin to estimate the longer-term effects this may have on CVD in the future.

Research Question:

Can medicines that are used to treat and/ or prevent CVD be used as a proxy to estimate the future burden of CVD events?

Rationale: We will use GPES extracts linked to dispensing data to estimate the change in prescribing in drugs used for the treatment and/ or prevention of CVD during the course of the COVID-19 pandemic. Knowledge of the patterns in the prescription of CVD drugs will inform understanding of the indirect impact of the COVID-19 pandemic on the control of CVD and its risk factors in the population, and can be used to model the likely impact on future CVD events in the UK population.

Objective 1: To describe patterns in monthly prescription and dispensing of CVD medicines before and during the COVID-19 pandemic; how these may vary from each other and according to other co-variates of interest such as sex, age, geographical region, ethnicity.

Study Population: The population resident in Wales, Scotland, England and Northern Ireland, aged 18 years or older registered with primary care practices who have opted into data linkage. Analyses will be restricted to individuals with the following criteria: (i) those registered with a primary care practice on or after 1 January 2018, (ii) had "GPES research quality acceptable" data at the time of study entry, (iii) aged 18 years or older on or after 1 January 2018, (iv) with recorded female or male sex, (v) with patient id available. Analysis end date will be the latest available monthly download at time of analysis.

Exposures: Medications will be extracted from the primary_care_meds and GDPPR (GPES Data for Pandemic Planning and Research) datasets. We will include medications commonly prescribed for CVD, diabetes, and their risk factors, following the BNF framework assigning medicines to their primary indication. BNF codes will mapped to relevant codes for extraction depending on the format of the dataset (e.g. SNOWMED in GDPPR). Date closest to prescription by GP/ dispensing to patient will be recovered (rather than system collection or processing date). We will initially focus on frequency of dispensing and prescribing (monthly counts); but subsequently consider the relevance of changes to medication quantity/ dosing/ scheduling.

Outcomes: This is primarily a descriptive rather than analytical analysis, although we will investigate how prescribing and dispensing patterns may vary according to other socio-demographic covariates

Covariates:

- Age (18-64; >=65 years old)
- Sex
- Geographical region / GP
- Ethnicity (where available)

Analyses: Monthly counts for prescribed, dispensed, proportion dispensed:prescribed medications will be calculated and presented for all individuals (primary analyses) for each CVD risk factor group and stratified by covariate sub-groups (secondary). R heatmap() / ggplot2 will be used to provide visualisations of the data (columns=months; rows=years).

Objective 2: To model disruption in trends in weekly prescription and dispensing of CVD medicines due to the COVID-19 pandemic at the population level using interrupted time-series analysis.

Study Population: The population resident in Wales, Scotland, England, and Northern Ireland, aged 18 years or older registered with primary care practices who have opted into data linkage. Analyses

will be restricted to individuals with the following criteria: (i) those registered with a primary care practice on or after 1 January 2018, (ii) had "GPES research quality acceptable" data at the time of study entry, (iii) aged 18 years or older on or after 1 January 2018, (iv) with recorded female or male sex, (v) with patient id available. Analysis end date will be the latest available weekly download at time of analysis.

Intervention: 31 January 2020 (first UK case of COVID-19) can be considered start of "intervention"; gradual slope change will be modelled to represent the onset of the pandemic in the UK through February-March 2020.

Outcome: Weekly counts for prescribed, dispensed, proportion dispensed:prescribed medications will be calculated for each CVD risk factor (following the same data preparation pipelines as Objective 1).

Analyses: Interrupted time-series analysis (ITS) will be used to model the population level changes in medication prescription/ dispensing trends following the onset of the COVID-19 pandemic (Lopez Bernal, J et al., 2017). Medications data prior to 31 January 2020 will be used to establish the counterfactual trend, providing a comparison against which to evaluate the impact of the pandemic. Analyses will be implemented in R and/ or Stata.

Covariates: A strength of ITS is that it is typically less affected by common confounding variables (e.g. age, sex etc.) as these change slowly over time. These will be taken into account during the modelling of the underlying long-long term trend, alongside relevant time-varying confounders (e.g. seasonality).