# INTRODUCING THE POTENTIAL OF POPULATION TARGETS TO DRIVE MORTALITY IMPROVEMENTS

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# 1 OUR NEED FOR MORTALITY MODELS

1.1 Modern societies need to determin when their citizens are liikely to die. Governments need accurate predictions to assess the infrastructure demands of their populations, the healthcare and social care needs of the ill and the elderly, and retirement ages that are equitable between the different generations. Pension funds, both public and private, need accurate predictions to ensure that they have adequate funds for their members' retirement needs.

1.2 Since the 18th century, actuaries have been tasked to make these predictions through the medium of mortality rates, assessing whether individuals at every age are more or less likely to die this year as compared to those who were the equivalent age last year (Pitacco, 2004).

1.3 The challenge for actuaries is that the future is unknown, and past trends are a poor guide for future trends. For example, massive reductions in childhood mortality during the 19th and mid 20th century through better sanitation, improved public health and the introduction of antibiotics could have exhausted the potential for further improvements or could have uncovered/inspired new areas for medical innovation and improvement (Griffiths and Brock, 2003; Shrestha, 2005).

1.4 For many years, actuaries subscribed to the theory that there was a biological limit to life expectancy, and that higher-than-expected rates of mortality improvement would limit the possibility of further mortality improvements. Future rates of mortality improvement were expected to eventually decline to zero.

## EXPLANATORY POWER OF COHORT-BASED MODELS

1.5 However, during the late 1990s it became clear that actual mortality improvements were significantly and consistently higher than predictions made only several years before. Prior actuarial mortality models had only ever considered two variables – attained age and calendar year (Lee, 2000).

1.6 Detailed analysis by Willets (2004) identified that these prior models had been too simplistic, and that those born in the early 1930s were showing much higher mortality improvements throughout their lives than the generations born before and after.

1.7 Willets' seminal actuarial paper proposed mortality models that considered year of birth as well as attained age and calendar year. The paper illustrated that such models provided a better fit for recent mortality experience and predicted much higher rates of mortality improvement in the first decade of the new millenium.

1.8 The paper sparked widespread interest in improving collective understanding of mortality trends both inside and outside the actuarial profession (Blake et al., 2006; Cairns et al., 2009), and accelerated the replacement of defined benefit with defined contribution pension schemes (Broadbent, Palumbo and Woodman, 2006) as pension schemes re-assessed future financial commitments that they had made to members on final salary schemes..

1.9 Demographers, such as Oeppen and Vaupel (2002), were particularly interested by the cohort analysis presented by Willets. Demographers are more circumspect in identifying cohorts as an explanatory factor for mortality differentials, and look for evidence of circumstances at or prior to birth that would be expected to affect the future trajectory of mortality. The most frequently cited example is the siege of Leningrad, USSR in 1944 where those born during the siege have shown higher mortality and earlier onset of cardiovascular disease throughout later life compared to those born earlier (Sparén et al., 2004)

1.10 The pertinent question is whether differences in mortality improvements between generations are as a result of circumstances at or near birth, or the cumulative result of behavioural changes and/or medical interventions that happened to impact one generation more than others because of their age at a particular time. For example, new clinical guidance might stipulate that a recently developed drug should be used proactively in the treatment of those over a certain age, and hence confer a significant advantage on those who happened to be crossing that age threshold at exactly that time.

1.11 We will henceforth refer to such instances as "age-period interactions". It is now increasingly accepted that the cohorts born in the early 1930s have benefitted from a succession of age-period interactions, with other developed countries showing similar patterns.

1.12 These age-period interactions are by no means limited to the distribution of new treatments. In fact, perhaps the most intensively investigated example of age-period interactions was the widespread reduction in the prevalence of smoking from the 1970s onwards, following successive publications on the dangers of smoking, including the British Doctor Study (Doll et al., 2004). The favoured cohorts that Willets identified experienced a faster rate of change in the dose exposure to cigarettes as compared to those born before and after.

1.13 Moreover, mortality experience from insurance companies comparing smoker and non-smoker lives found that the cohort born in 1926 showed the highest rates of mortality improvement. This would be consistent with higher socio-economic groups showing an earlier propensity to give up smoking (Davy, 2007).

# 2 EXPLANATORY MODELS OF HISTORICAL MORTALITY TRENDS

2.1 This renewed interest in understanding mortality trends has shifted the collective focus from mortality models, such as Lee Carter, that project future mortality rates without consideration of biological plausibility to explanatory models. Such explanatory models can be grouped into two categories: (1) those that attempt to explain historical trends in terms of observed changes in risk behaviour and accessibility to treatment/care and (2) those that attempt to predict future trends in terms of anticipated changes in risk behaviour and available treatments/healthcare.

2.2 Explanatory models make much greater demands in terms of modelling capabilities and data inputs, such as population risk factors, healthcare utilisation and disease prevalence. Given the number of different causes of death and the increasing specialisation of healthcare through secondary and tertiary care, researchers have tended to limit their explanatory models to a subset of causes of death, such as the CONCORD studies that attempted to explain differences in international cancer survival.

2.3 The research group at the University of Liverpool led by Professor Capewell developed an explanatory model of the first category, focused on coronary heart disease (CHD). Their IMPACT model is a Excel cell-based model that compares how observed age-specific mortality rates have changed between two selected years, as against changes in the prevalence of risk factors and availability of treatments over the period between the years.

2.4 One of the first applications of the IMPACT model was evaluating changes in the number of CHD deaths in England and Wales between 1981 and 2000 against changes in selected population risk factors and changes in available medical and surgical interventions over that period (Capewell, Unal and Critchley, 2004). The IMPACT model methodology has proven to be robust and highly replicable as the necessary data is generally available from public health data sources without requiring access to or analysis of electronic health records. The model is not onerous in its demands, as it neither gathers mortality data on the intervening years nor attempts to explain the observed pattern of mortality improvement rates during the intervening period.

2.5 The risk factor variables considered in that study were smoking, total cholesterol, blood pressure, obesity, diabetes, physical activity and social deprivation. For the first three risk factors, regression coefficients from the MONICA study were applied to the observed relative reduction in each risk factor and the number of CHD deaths in the initial year to determine the reduction in the number of CHD deaths in the last year. For the latter four risk factors in the absence of suitable regression coefficients, the population attributable risk fraction method was used according to the following formula:

- Population attributable risk fraction = (prevalence of risk factor) * (relative risk -1) / (((prevalence of risk factor) * (relative risk -1))+1)

2.6 Separate interventions were considered for each of the following forms of CHD: acute myocardial infarction, chronic angina, unstable angina, heart failure, hypertension. For each intervention, an expected mortality reduction was calculated based on (1) change in prevalence of usage between the start and end years of the observation period, (2) reported survival benefits estimated from meta-analyses and randomised controlled trials (RCT). Allowance was made for the likelihood of medication non-adherence and the impact of polypharmacy. Polypharmacy typically refers to patients being prescribed 5 or more medications to manage multiple conditions. The complete list of interventions was as follows:

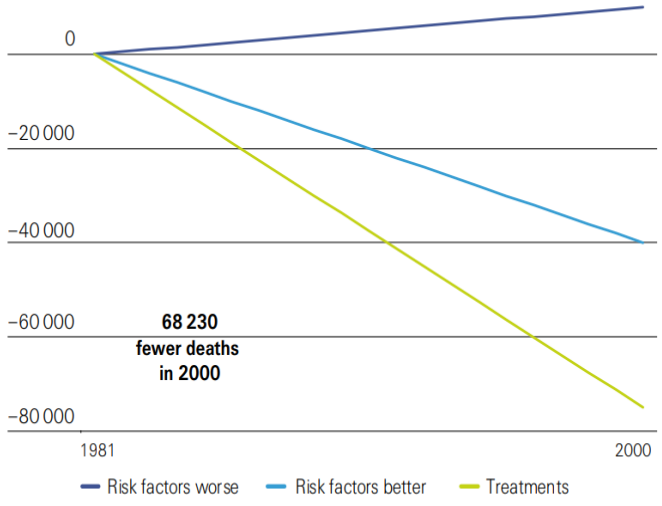
- Acute myocardial infarction – resuscitation, thrombolysis, aspirin, primary angioplasty, beta-blockers, ACE inhibitors, statins, warfarin

- Chronic angina – CABG surgery, angioplasty, aspirin
- Unstable angina – aspirin, heparin, platelet inhibitors
- Heart failure
- Hypertension management – beta blockers, ACE inhibitors, diuretics, calcium channel blockers

+ primary prevention targeted on at-risk cohorts, such as statins.

2.7 Figure 1 compares the numberr of deaths between 1981 and 2000, and estimates what percentage of the change was caused, prevented or postponed as a result of changes in risk factors and in treatment usage (Capewell, Unal and Critchley, 2004). Further information on the data sources used is set out in the Appendix.

## Figure 1 – Impact of risk factors and treatment on reducing mortality in England & Wales between 1981 and 2000




| | |
|---|---|
| Risk factors worse | +13% |
| Obesity (increase) | +3.5% |
| Diabetes (increase) | +4.8% |
| Physical activity (less) | +4.4% |
| Risk factors better | −71% |
| Smoking | −41% |
| Cholesterol | −9% |
| Population BP fall | −9% |
| Deprivation | −3% |
| Other factors | −8% |
| Treatments | −42% |
| AMI treatments | −8% |
| Secondary prevention | −11% |
| Heart failure | −12% |
| Angina: CABG & PTCA | −4% |
| Angina: Aspirin etc | −5% |
| Hypertension therapies | −3% |

Source: Unal (2004), Circulation

2.8 Figure 1 illustrates that almost all of the observed mortality changes could be ascribed to either net changes in risk behaviour (~60%) or to changes in treatment usage (~40%). The most significant contributor was changes in the prevalence of smoking, which was estimated to be responsible for 41% of the reduction in number of CHD deaths over this period.

2.9 Different groups of researchers have applied the IMPACT methodology to different countries/sub populations (Hotchkiss et al., 2014; O'Flaherty et al., 2016). Although the estimated contribution from different risk factors and treatment usage varies between different country assessments, the common finding is that the main driver of mortality improvements over the last 40 years was massive reductions in the number of smokers in the population.

2.10 By way of verifying this finding, Swiss Re developed an alternative model to determine the proportion of historical mortality improvements that could be ascribed to changes in

smoker status. This model was based on data from the series of UK General Household Surveys (1972-2004) that records age, sex and smoking status (current smoker, ex-smoker, never smoker) on all respondents, and derived mortality rates for each smoking status group from annual reported aggregate population mortality and mortality differentials between different smoking statuses (reported in the British Doctors Study).

2.11 Table 1 sets out rates of aggregate mortality improvement by decade and decennial age group for men from this model, as reported in Rischatsch (2018). The analysis confirms that 30-50% of male mortality improvements during the period 1972-2004 were driven by changes in smoking status.

**Table 1: Contribution to male annual mortality improvements from change in smoker status - UK males, 1972-2004, (Rischatsch, 2018)**

| | Annual mortality improvement | | | | | | |
|---|---|---|---|---|---|---|---|
| Age group | 1970s | 1980s | 1990s | 2000s | Average (total) | Average (from change in smoker status) | Contribution (from change in smoker status)* |
| 20s | 1.2% | -0.1% | 0.2% | 3.0% | 0.7% | 0.1% | 16% |
| 30s | 1.6% | 0.0% | -0.1% | 1.5% | 0.5% | 0.2% | 44% |
| 40s | 2.2% | 2.0% | 1.0% | 0.9% | 1.6% | 0.7% | 45% |
| 50s | 1.4% | 3.0% | 2.4% | 2.2% | 2.3% | 0.9% | 39% |
| 60s | 1.5% | 2.0% | 3.2% | 3.4% | 2.4% | 0.8% | 34% |
| 70s | 1.3% | 1.7% | 2.3% | 3.8% | 2.1% | 0.7% | 32% |
| 80s | 0.6% | 1.2% | 1.3% | 2.5% | 1.3% | 0.2% | 19% |

# 3 PREDICTIVE MODELS OF FUTURE MORTALITY TRENDS

3.1 Since 2011, mortality improvements have been lower than expected in many developed countries (Hiam et al., 2018). Governments, healthcare professionals and public health experts are keenly interested in whether mortality improvements in the future will return to the rates seen in the 2000s. Further, whether such reversal could be most efficiently achieved through promotion of healthy behaviours, restriction of unhealthy behaviours or greater focus on preventative strategies and improved access to primary care.

3.2 As described earlier, the second category of explanatory models attempt to predict future trends in terms of anticipated changes in risk behaviour and available treatments/healthcare. Various research groups have used the IMPACT methodology to assess the impact on mortality of putative health policies, either directed at changing future prevalence of risk factors (Critchley and Capewell, 2003) or improved compliance with clinical guidelines for treatment (Capewell et al., 2006). Such studies described future trajectories or scenarios, and their success can be evaluated in the light of later experience.

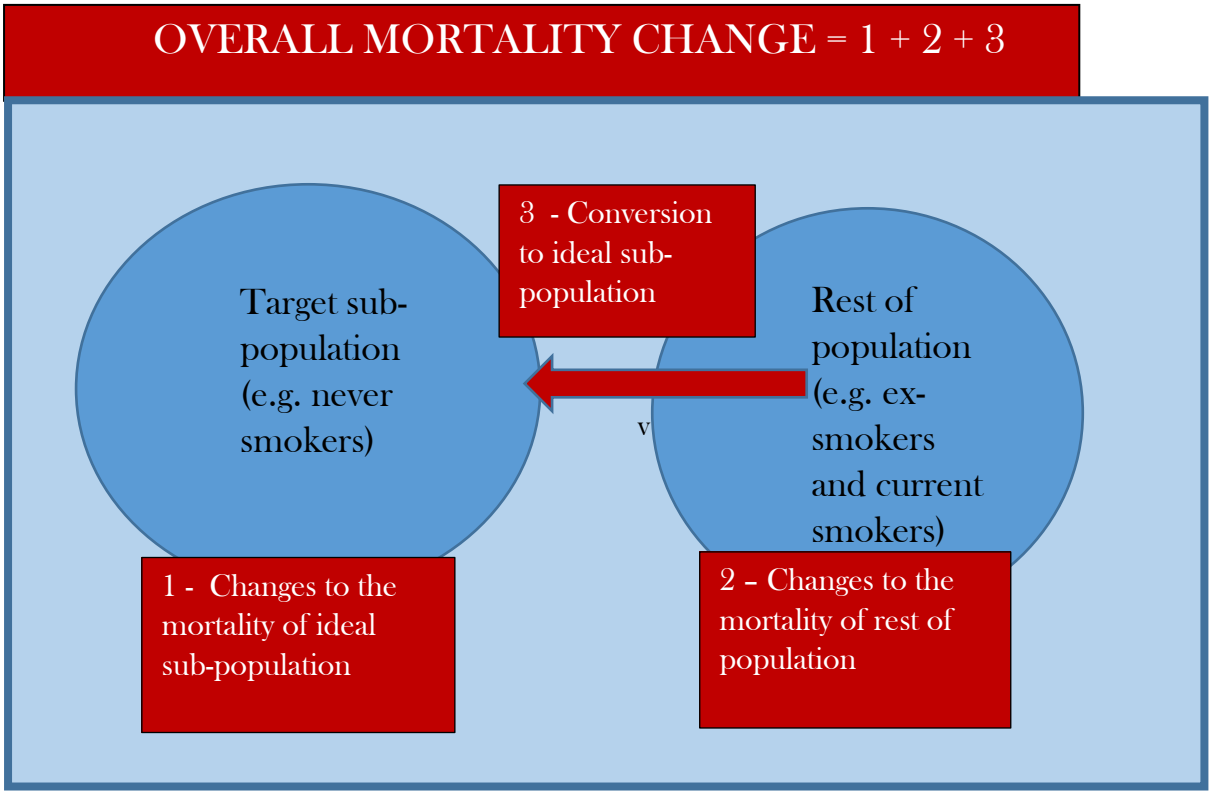
3.3 It is perhaps instructive to consider that most health policies are structured around the identification of an ideal sub-population whose health characteristics are superior to the aggregate population. The healthcare system then aims to improve the morbidity and mortality experience of those not in the ideal sub-population through the promotion and provision of behavioural and pharmaceutical interventions. By way of illustration, the British Doctor Study (Doll et al., 2004) identified never smokers as an ideal sub-population. The study quantified that current smokers have double the mortality of never smokers. Further, the relative mortality of ex-smokers as compared to current smokers improves with each year after smoking cessation.

3.4 These findings galvanised healthcare professionals and society to improve population health through smoking cessation. Multi-dimensional interventions were designed and implemented to encourage and maintain smoking cessation, including nicotine replacement therapy, support groups, advertising restrictions, health promotion and sales taxes. The result has been the steady improvement in the morbidity and mortality experience of an increasing prevalence of ex-smokers, without any overt benefits to never smokers. The introduction of e-cigarettes and vaping will continue to drive improvements for current smokers, notwithstanging concerns over the widespread adoption by young adults in the USA who were never-smokers.

3.5 Building on this example, we can propose a Markov state model of population mortality change ("MSMPMC") as illustrated in Figure 2, where aggregate mortality changes can be deconstructed into the following 3 elements:

1) Mortality changes that are only experienced by the ideal sub-population, whether because of changes in behaviour, exposure or treatment, or any combination of these elements.
2) Mortality changes that are only experienced by those outside the ideal sub-population.
3) Mortality changes that follow from eliminating health differences between a proportion of the rest of the population and the ideal sub-population.

**Figure 2 – Markov state model of population mortality change ("MSMPMC")**




## CHOOSING BETWEEN IMPACT AND MSMPMC

3.6 Given the widespread usage of the IMPACT methodology, it is appropriate to consider whether it is necessary to develop a separate methodology such as MSMPMC to model the benefits of conversion to an ideal sub-population. Moreover, it is good practice to consider in more depth the advantages and disadvantages of each methodology for a range of purposes. These are set out in Table 2.

3.7 The first key limitation of the IMPACT methodology is that it only considers changes between two timepoints. As such, it would require a series of sequential models to provide a more realistic picture of the pattern of mortality changes over time. The second key limitation is that the deconstruction of mortality changes into changes in individual risk factors and in treatment interventions means that it is difficult to track the experience of different populations, unless the sub-populations can be defined by a single risk factor or treatment intervention. Both limitations were deliberate choices on the part of the creators at Liverpool University as these limitations reduce the data and computing demands of the methodology, and were appropriate for the early 2000s.

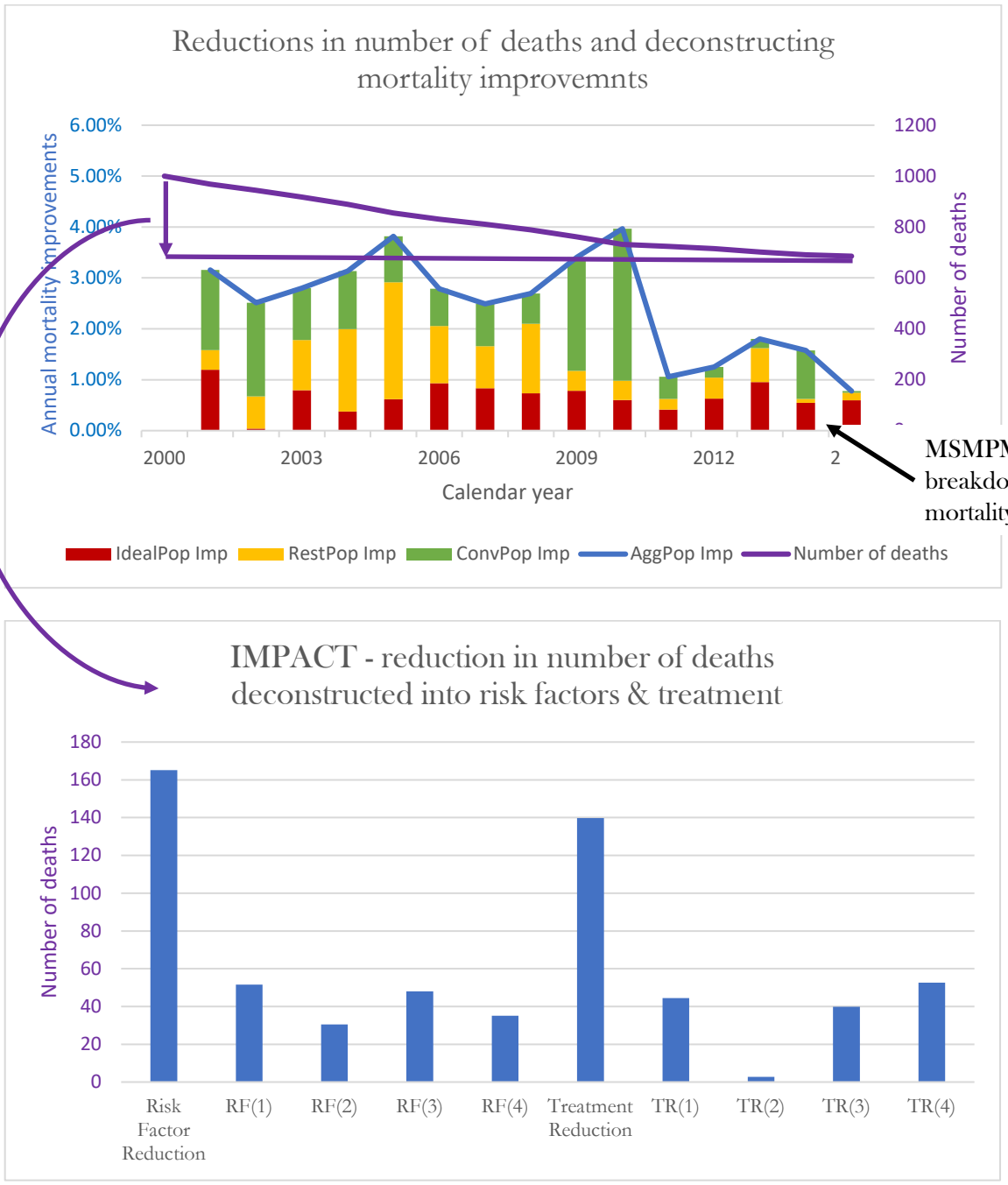
3.8 However, the increasing availability of large longitudinal datasets of individual patient electronic health records, particularly in the UK, and increased computational power mean that more complicated sub-populations can be relatively easily defined, grouped and tracked over periods up to a decade or more. In addition, the quality of datasets such as the Clinical Practice Research Dataset (CPRD) and The Health Improvement Network (THIN) has been continuously improving because of auditing requirements of the Quality Outcome

Framework (QOF) that first introduced clinical performance targets in 2003 for general practitioners in England & Wales.

## Table 2 – Comparison of features between IMPACT and MSMPMC models

| FEATURES | IMPACT | MSMPMC |
|---|---|---|
| **Key data sources** | Cause of death statistics; prevalence of risk factors; treatment usage | Electronic health records |
| **Data complexity** | + | +++ |
| **Computation complexity** | + | +++ |
| **Time step** | Single multi-year transition | Multiple transitions of any period |
| **Functional unit** | Individual risk factors or treatment classes | Sub-populations through any combination of diseases, risk factors, biomarkers or treatments |
| **Ability to project mortality** | Yes, for a defined period | Yes, for any future periods |
| **Ability to project morbidity** | No | Yes, for all future periods |

**Figure 3 – Contrasting presentations of mortality improvement - IMPACT vs MSMPMC**




3.9 The IMPACT model is the most appropriate for determining the benefits of smoking cessation because the sub-populations can be defined through reference to a single risk factor, the limited number of categories and the fact that we are interested in the cumulative benefit over time. For sub-populations that are more complicated to define or where we

are interested in the time pattern of mortality improvements, a MSMPMC may be more suitable if appropriate data exists and can be obtained at a reasonable cost.

3.10 These considerations prompt two further questions. First, what other desirable and attainable sub-populations could be defined and provide a basis to promote and support drives to improve population health? Second, how effective and efficient would be the process of narrowing differences in health characteristics between sub-populations as compared to, for example, improving the treatment of those with a particular disease or vaccinating an entire population against particular infectious diseases?

3.11 In selecting suitable ideal sub-populations, we can draw on the series of disease prevalence studies carried out by the Institute of Health Metrics and Evaluation at the University of Washington under the overall aegis of the Global Burden of Disease. These studies provide a global and in-depth understanding of the relative importance of up to 67 risk factors in countries (and some sub-countries) around the world (Lim et al., 2012). The Global Burden of Disease assesses and projects mortality rates, the prevalence of morbidity and the prevalence of disability. Tobacco smoking and hypertension are rated as the two highest ranked risk factors for causing years of disability globally.

3.12 There is still potential for significant mortality improvements from smoking cessation in developing countries because of continuing high rates of smoking, particularly amongst men. However, there is much less potential in developed countries and as such there would be little to be gained from the deeper understanding that would be provided by a MSMPMC. In contrast, although we have known about the perils of hypertension for as long as smoking, changing guidelines and poor adherence mean that there is still likely to be significant potential for mortality improvements from more effective hypertension management. Before putting forward a proposal for a MSMPMC, it is appropriate to provide some historical context on the epidemiology of hypertension.

# 4 IMPORTANCE OF HYPERTENSION MANAGEMENT TO FUTURE MORTALITY TREND

4.1 Hypertension has been described as the "silent killer" because it causes no symptoms. Hypertension has been identified as a key risk factor for atherosclersosis and stroke since the 1920s (Sawicka et al., 2011). Increasing concerns over the burden of hypertension led to the establishment of the Framingham study in the US in 1948, and more recently offspring studies involving 2nd and 3rd generations.

4.2 Studies based on the Framingham cohort have elucidated that hypertension is the main risk factor for both ischaemic and haemorrhagic stroke (D'Agostino et al., 1994) and that there is a dose-relationship between high blood pressure and both the likelihood and severity of stroke with no lower limit (Ravenni et al., 2011).

4.3 It is an indication of how long the Framingham study has been running that there was no effective treatment for hypertension in the 1950s, and therefore longitudinal data could be collected on subjects with unmanaged hypertension. Such a protocol would not be ethically acceptable today. The PRoFFESS study determined that the risk of stroke incidence could be significantly controlled by optimal anti-hypertensive treatment (Grassi et al., 2009).

4.4 Given this history and the continued risk of hypertension as evaluated by IHME, it would be reasonable to consider that normotensives (those with normal blood pressure) could be regarded as a further target sub-population, and that the narrowing of mortality differentials between hypertensives and normotensives could be a continuing source of mortality improvements in different countries around the world.

4.5 In the UK, the National Institute of Healthcare and Clinical Excellence (NICE) produces clinical guidelines that are intended to evaluate and set standards of best clinical practice for the treatment of specific diseases. Since 2003, general practitioners have been evaluated against Quality Outcome Framework (QOF) and are financially rewarded for good practice against multiple indicators in different domains (Gillam and Siriwardena, 2018). As such QOF could be a strong driver to clinical practice(Doran et al., 2014).

4.6 NICE published NG136 in August 2019 on the diagnosis and management of hypertension in adults (Boffa et al., 2019), replacing the previous guideline CG127 published in August 2011. NG136 provides guidance on age-specific and condition-specific targets for systolic and diastolic blood pressure, and the sequencing of treatments that should be considered.

4.7 For example, the targets for those under age 55 without diabetes are 140/90mmHg and the recommendation for those with higher blood pressure starts with lifestyle advice, followed by first line treatment with either an ACE inhibitor or angiotensin-receptor blocker and second line treatment with either a calcium-channel blocker or diuretic. These lifestyle changes would include weight reduction, regular exercise, reduced salt in the diet, quitting smoking, limiting caffeine and alcohol intake and reducing levels of stress in daily life (Uzun et al., 2009).

4.8 The detailed nature of the clinical guidance and the financial incentives provided for rewarding opctimal linical practice might suggest that hypertension management was already optimal in the UK and that there was little opportunity for further mortality improvements from this source. However, optimal treatment requires both compliance by general practitioners and adherence (to both medications and lifestyle changes) by patients. The challenge and the opportunity is that levels of adherence are lower than might be expected (Sabaté, 2003).

4.9 The multiple prescription strategy outlined in the NICE clinical guidance leads to complex regimens with patients failing to take the correct dose because of forgetfulness, lack of

undersatnding, inconvenience or side-effects (Ingersoll and Cohen, 2008; Guthrie et al., 2015). Simplification of regimens, behavioural reminders, strong social networks, supportive carers, repacking of medications (e.g. Pillpack) can be potent drivers of improved adherence, helped by technology such as smart containers, motion sensors and ingestible pills (-> Impact on insurance of medication adherence).

4.10 Our research will focus on the extent to which better hypertension management could lead to untapped sources of mortality improvement, and consider how effective and efficient various different types of intervention, programs and incentives can be in achieving optimal care as compared to other healthcare expenditure. This would need to address both clinical practice and compliance on the part of the healthcare professionals and attitudes and adherence on the part of the patients.

4.11 Electronic health records (EHR) could provide data on blood pressure measurements (both at the surgery and monitoring at home), incidence of stroke, progression of co-morbidity and eventual death. In addition, the prescribing record provides medication types and dosing levels. It is not possible to assess levels of non-adherence directly but it is possible to determine when the patient would have access to the medication through the history of dispensed medications and combine this with disease-specific surveys on self-reported adherence rates.

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# 6 APPENDIX

6.1 The following list sets out the different sources that were used by the England & Wales IMPACT model to provide data on prevalence, incidence and trend information on different CHD conditions and their treatment:

- Myocardial infarction incidence from British Heart Foundation
- Number of patients admitted to hospital with myocardial infarction, angina or heart failure from Hospital Episode Statistics
- Patients undergoing coronary artery bypass graft (CABG) or angioplasty from UK Cardiac Surgical Register and British Cardiovascular Intervention Society nidentified the numbers of patients admitted to hospital with myocardial infarction, angina and heart failure from Hospital Episode Statistics
- Number of patients in the community with treated or untreated hypertension or angina from 1998 Health Survey for England and British Regional Heart Study
- Treatment prescription and uptake from national audits and surveys
- Population risk factor trend from British Regional Heart Study, the General Household Survey and the Health Survey for England.
- Efficacy of interventions and mortality reduction from changes in cardiovascular risk factor from RCTs and cohort studies.