Which combinations of Multiple Long-Term Conditions (MLTC) are associated with the greatest risk of hospital admission over the winter season, and to what extent does COVID-19 or influenza vaccination modify this risk?

Background: More than 25% of people in England are living with two or more Long-Term Conditions (MLTC) (Cassell et al, 2018). Our group's recent systematic review showed that the care needs for people with MLTC account for >50% of primary and secondary care costs, and a significant part of community and social care costs (Dambha-Miller et al,2022). People with MLTC are at a higher risk of hospitalisation, especially during the winter season, with those aged over 65 years, females, ethnic minorities, and socioeconomically deprived groups sharing a disproportionately higher burden of poor outcomes (Tran et al.,2022). While it is well established that an increasing number of MLTC is associated with a higher risk of hospitalisation, it is unclear which combinations of MLTC are associated with greatest risk. Previous studies have included only a limited number of conditions or considered higher level groupings of conditions such as cardiovascular, respiratory or endocrinology disease, rather than exploring the granularity of individual diseases in combination. More detailed understanding of risks of hospitalisation and death from combinations of individual disease in MLTC could inform targeted interventions and prioritisation of resources (such as vaccination) within the limited time period before this winter season. The current approach to intervention such as influenza vaccination is broad including anyone over 65 years or with any 10 specified clinical conditions but does not yet consider combinations of specific diseases. Given the annual challenges in achieving high vaccination rates in time for the winter, highlighting specific at-risk groups may inform prioritisation of interventions including vaccination for rapid delivery to those who might benefit the most during this winter season. Our group recently led a consensus document amongst researchers in MLTC across 12 institutions in the UK agreeing on 59 conditions under the umbrella term of MLTC (Dambha-Miller et al.,2022). This was based on extensive work by Guthrie et al, and it is this list of conditions that will be considered. As the number of MLTC increases, the possible combinations of MLTC become exponentially larger. Therefore, analysis involving all combinations of MLTC, when conducted at the whole-population level with >65 million unique patients, requires in-depth knowledge and experience of the big data science pipeline, and powerful computational and analytical resources. Our interdisciplinary team has established these resources and the necessary expertise through existing multi-million-pound NIHR and MRC investment. We will leverage our existing resources and the expertise of our current team to deliver this important work on time to improve care this winter season.

Methods: We will use General Practice Extraction Service Data for pandemic planning and

research (GDPPR) within a trusted research environment (TRE) established by NHS Digital and Health Data Research UK (HDRUK). This is the only dataset that includes all adults in England who are registered with a GP practice. This data has already been linked to a range of critically important datasets such as hospital episode statistics (HES) including emergency, and admitted patient care data (APC), ONS-linked mortality, and national immunisation data. This means that we have the necessary variables of interest in already established environments ready for analysis.

Analysis: We will apply a combination of data science techniques to minimise the data and computational complexity in consultation with practising clinicians and members of the patients and public. As noted above, one of the critical analytic issues is the number of possible MLTC combinations. For example, with only 35 of our proposed 59 MLTC (35 is the recommended minimum number of MLTC to be reported as per a recent consensus study by Ho et al.2022), the total number of combinations with at least two MLTC exceeds 34 billion. Therefore, we will apply data science tools to identify the most frequent combinations of MLTC. Once the MLTC combinations are identified, we will use conventional statistical models to estimate the risk of specified outcomes associated with each MLTC combination.

Our primary outcome of interest is all-cause hospitalisation. Our secondary outcomes are cause-specific hospitalisations and mortality. Our primary objective is to estimate the true burden on healthcare (rather than individual risk of hospitalisation or deaths). Therefore, we will include all instances of hospitalisation, and use overdispersed Poisson regression models to estimate the incidence rates of hospitalisation. The log of the follow-up time will be used as an offset term in the model. To ensure statistical efficiency and precision of the parameter estimates, our primary analysis will be restricted to MLTC clusters with at least 50 outcomes (so that we could additionally adjust for age, sex, ethnicity, and deprivation).

We will apply causal mediation analysis to estimate the direct effects of the MLTC combinations and the proportion of excess rate of hospitalisation that could be mediated (and potentially alleviated) through vaccination against COVID-19 and seasonal influenza. We will repeat these analyses by age, sex, ethnicity, and deprivation to examine the inequalities in risks of these outcomes.

Patient and Public Involvement and Engagement (PPIE): We have an established PPIE departmental panel. We have identified two people living with MLTC whom we have consulted in our project inception and in the draft of our plain English summary. We will continue to seek input across the lifecycle of our work through data interpretation, dissemination, and knowledge translation. We have included costing for our PPIE to attend all our fortnightly team meetings and input on dissemination material including scientific papers, plain English summaries, and video abstracts. They will be supported by a named department PPI lead (Sonia Newman) and acknowledged with appropriate honorary contracts and authorship on outputs.