Multimorbidity: Cross-sector opportunities for developing new interventions for patients with multiple long-term conditions

Summary of a FORUM workshop held on 19 & 22 October 2020

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The Medical Research Council (MRC) improves the health of people in the United Kingdom (UK) - and around the world - by supporting excellent science, and training the very best scientists. The MRC is part of UK Research and Innovation (UKRI).

The MRC's mission is to:
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- produce skilled researchers
- advance and disseminate knowledge and technology to improve the quality of life and economic competitiveness of the UK
- promote dialogue with the public about medical research

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The National Institute for Health Research (NIHR) is the nation's largest funder of health and care research. The NIHR:
- Funds, supports and delivers high quality research that benefits the NHS, public health and social care
- Engages and involves patients, carers and the public in order to improve the reach, quality and impact of research
- Attracts, trains and supports the best researchers to tackle the complex health and care challenges of the future
- Invests in world-class infrastructure and a skilled delivery workforce to translate discoveries into improved treatments and services
- Partners with other public funders, charities and industry to maximise the value of research to patients and the economy

The NIHR was established in 2006 to improve the health and wealth of the nation through research, and is funded by the Department of Health and Social Care. In addition to its national role, the NIHR supports applied health research for the direct and primary benefit of people in low- and middle-income countries, using UK aid from the UK government.

The Academy of Medical Sciences

The Academy of Medical Sciences is the independent body in the UK representing the diversity of medical science. Our mission is to promote medical science and its translation into benefits for society. The Academy's elected Fellows are the UK's leading medical scientists from hospitals, academia, industry and the public service. We work with them to promote excellence, influence policy to improve health and wealth, nurture the next generation of medical researchers, link academia, industry and the NHS, seize international opportunities and encourage dialogue about the medical sciences.

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, or its Fellows.

All web references were accessed in August 2021.

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Executive summary

As we live longer, more of us are likely to suffer from multiple long-term health conditions (MLTC). An estimated 54% of people over the age of 65 in the UK already have MLTC. The prevalence of multimorbidity is expected to increase to two-thirds of all adults aged over 65 by 2035.

However, despite this trend, the majority of biomedical research is still 'single-system' focused, looking at understanding and treating single diseases or diseases that affect a single organ. Coupled with this, the way in which healthcare is delivered is similarly single-system focused, treating a patient without always incorporating a holistic approach that could account for and accommodate other co-existing conditions. As a result, patients are increasingly taking multiple medications at the same time (polypharmacy), with clinicians often making treatment decisions with incomplete information about the benefits and harms of concurrent treatments. From a research perspective, this single-system approach means that scientists may miss opportunities to find and develop treatments that target common pathways.

In June 2020, the Academy of Medical Sciences, the Medical Research Council (MRC), the National Institute for Health Research (NIHR) and the Wellcome Trust published a framework that outlined some of the priorities for multimorbidity research that would help lead to better understanding of MLTC, and enable the development of new treatments to better address them.[1]

Following this, on 19 and 22 October 2020, the Academy of Medical Sciences, the MRC and the NIHR held a workshop to examine the respective opportunities and challenges for three priority themes amongst a cross-sector audience from academia, industry, the NHS, and the wider life sciences sector.

Workshop participants discussed the system-level considerations for supporting and facilitating MLTC research in all its forms, and incentivising and accelerating the development of interventions for patients with MLTC. A number of cross-cutting themes were identified:

- **Putting patients at the heart of MLTC research and trials**. Researchers need to understand what is important for patients in treating and managing their conditions and consider how these priorities can be built into the framework of MLTC research.
- **Reflecting on current clinical pathways and healthcare delivery to consider how the needs of patients with MLTC can be best met**. Clinical and policy-focused research to evaluate the impact of service delivery innovations and interventions on quality of care for people with MLTC could help tackle some of the everyday issues highlighted by patients.

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[1] Academy of Medical Sciences (2020). *Cross-funder multimorbidity research framework.* https://acmedsci.ac.uk/file-download/50613213

- **Creating a shared language through a common set of definitions, reporting systems, and standards**. Multimorbidity research is fragmented and requires collaboration across different disease areas and fields. A shared language between researchers and clinicians across the life sciences sector would help improve communication and collaboration.
- **Developing skills and training related to MLTC for researchers and clinicians**. A paradigm shift from single disease to MLTC research and treatments will also require a parallel shift in skills, for both clinical and non-clinical researchers. There is a need to assess the skills gaps and training needs.
- **Bringing single disease and national research funders, societies, charities and publishers together to make progress on priorities**. Such organisations can provide clarity and focus for the most promising MLTC research avenues and promote multimorbidity research through cross-disciplinary meetings, conferences and publications.
- **Supporting cross-sector collaboration and knowledge exchange through public-private partnerships.** Platforms and infrastructure to enable mutually productive cross-sector collaboration and knowledge exchange act as an integral research enabler and should be promoted.
- **Highlighting and celebrating exemplars of MLTC studies** that demonstrate success and feasibility will incentivise others to pursue similar research.
- **Placing greater emphasis on preventing the development of secondary and tertiary health conditions**. MLTC research is heavily focused on treatment and more could be done in the targeted prevention space, especially as each additional condition a person develops dramatically impacts their health and wellbeing.

Participants also discussed three MLTC research themes, derived from some of the research priorities outlined in the 2020 framework, in further detail, which are summarised below.

Theme 1: Data-driven approaches at the heart of understanding multiple long-term conditions – harnessing existing assets and creating new ones.

Adopting data-driven approaches to identify clinically relevant disease clusters, help inform research efforts, prioritise the most promising areas and understand patient populations to ensure research remains relevant. Priority areas identified at the meeting included:
- **Maximising the use of the UK's many rich data sources.** Such datasets are not always widely known about, or easily accessible to researchers. The community should work to raise awareness of available datasets and support researchers in accessing them. Datasets would benefit from improved metadata and interoperable systems to allow the linking of datasets.
- **Embracing distributed team science at scale**, including by utilising and extending existing resources and networks to facilitate access to real-world, cohort, trials and experimental data (both public and commercial) for UK and international teams.
- The need for **deep phenotyping in longitudinal cohorts**, including consideration of trajectory and severity of disease and defining phenotypes that influence outcomes from patient and health service perspectives.
- **Maintaining UK cohorts for MLTC research**, the combined value of which is far greater than the sum of their parts. A multi-funder approach should be considered to support cohorts to provide access for research that focuses on MLTC rather than single diseases or outcomes.

- **Encouraging collaboration between data scientists, clinical researchers, and service users and patient communities** and improving understanding of their distinct roles. These communities need to come together to develop their knowledge of MLTC and consider the meaningfulness of disease clusters and the research opportunities they present.

Theme 2: How understanding biological pathways is providing new opportunities to develop interventions.

Understanding the biological mechanisms that link disease clusters provides new opportunities for drug development or drug re-purposing, and reveals novel drug targets for treating multiple conditions with single pathways, thereby reducing polypharmacy. Priority areas identified at the meeting included:
- The need to **continue to develop translational technologies that will support mechanistic research** (such as animal models and organoids), and to better engage fundamental and drug discovery researchers in MLTC research.
- The need to **triangulate multiple evidence sources to de-risk novel drug targets for industry** as targeting multiple diseases is very high risk. Good evidence would involve triangulation of data from *ex vivo* models, epidemiology and animal models. Greater use of artificial intelligence (AI) and modelling may help to confirm or identify new targets.
- **Key evidence sources can be used for developing hypotheses and facilitating a reverse translation approach.** Evidence sources include existing cohorts, big data repositories, and programmes in the human experimental medicine space.[2]
- The **importance of collaboration between academia and industry** was strongly highlighted. In particular, working collaboratively on drug targets rather than specific diseases in order to treat MLTC with drugs that target common pathways.
- The **importance of defining the clinical development pathways early on**, so that appropriate endpoints are used (e.g., in trials) that are relevant for MLTC, rather than individual diseases. Discussion with regulators and cross-sector alignment would be needed to redefine these endpoints over time.

Theme 3: How do we facilitate clinical trials that are inclusive of patients with MLTC?

Incorporating patients with MLTC, who are the population most likely to be seen by clinicians, into clinical trials will ensure that treatments are proven effective and safe in these patients. Key points identified at the meeting included:
- The need to **put patients at the centre of trial design and delivery**. Simpler trials that are more focussed and inclusive are needed, delivered in ways that are convenient to patients.
- **Exclusion of patients with MLTC is closely related to other forms of inequity in access to trials**. Populations who get excluded for socio-economic reasons are often those with MLTC. Solutions to engender trust and co-production, with strong patient and public involvement, are required.
- The need to **capture and report comorbidities in a standard way**, both in research delivery systems and trial reports.

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[2] Reverse translation, also known as 'bedside to bench' research, refers to using research approaches typically found in the later stages of drug development to inform earlier stages. For example, using insights from experimental medicine, clinical practice and patient experience to better inform drug discovery programmes and prioritisation, or by using animal models as a tool to inform basic science and target selection.

- The **need to bring stakeholders and diverse clinical networks together** to cut across silos, developing 'exemplar projects' as a starting point.
- Funders have a critical role to play to stimulate MLTC trials. Given the pressures that some funders are facing because of COVID-19, **innovative collaborations between funders** could be timely.
- **The importance of speaking to regulators early** to agree on designs for MLTC trials and possibly to define exemplar protocols. **The Medicines and Healthcare products Regulatory Agency (MHRA) could develop a 'points to consider' document for MLTC trials**, which would act as the basis for discussions between regulators and sponsors about how MLTC are handled in regulatory submissions.

Introduction

An estimated 54% of people over the age of 65 in the UK have multiple long-term health conditions (MLTC), often referred to as multimorbidity.[3] As our population ages, the prevalence of MLTC is expected to increase to two-thirds of all adults aged over 65 by 2035.

Despite growing evidence for the occurrence of common 'clusters' of chronic diseases, a lack of understanding of the biological mechanisms underlying these clusters and viable drug targets, as well as difficulties of conducting clinical trials with patients with multiple conditions, all limit the ability to develop treatments for MLTC. As a result, most treatments still typically target single conditions, with little consideration of the underlying root causes within disease clusters.[4] Together with a paucity of evidence-based, implementable medical guidance on MLTC, this increases the likelihood of polypharmacy and associated adverse drug reactions (ADRs). ADRs themselves are a significant contributing cause of morbidity, and have been estimated to account for up to 8% of unplanned hospital admissions in the UK,[5] costing the NHS approximately £1 bn–£2.5 bn annually.[6] COVID-19 has further highlighted these issues; we know that people with certain long-term conditions are at risk of poorer outcomes from COVID-19, and it has been suggested that having MLTC is an indicator of severe adverse outcomes (see Annex I for an overview of research priorities in the context of COVID-19 and MLTC provided by Professor Kamlesh Khunti FMedSci, Professor of Primary Care Diabetes and Vascular Medicine at the University of Leicester, and Professor Alan Silman FMedSci, Professor of Musculoskeletal Health at the University of Oxford at the workshop). We therefore need to better understand the patterns and drivers of interactions between conditions in relation to outcomes for patients with MLTC.

In 2018, the Academy of Medical Sciences produced a working group report that set out a series of research priorities to help realise the ambition of understanding and treating MLTC in a way that maximises benefits to patients while minimising potential harms.[7] Following the publication of the report, the Academy, the Medical Research Council (MRC), the National Institute for Health Research (NIHR) and the Wellcome Trust developed a cross-funder multimorbidity research framework, which aims to help co-ordinate the efforts and initiatives in which the various funders are engaged, and drive forward the multimorbidity research agenda in the UK and globally.[8] Following this, three

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[3] Kingston A, *et al.* (2018). *Projections of multimorbidity in the older population in England to 2035: Estimates from the Population Ageing and Care Simulation (PACSim) model*. Age and Ageing **47(3)**, 374-380.

[4] Fortin M, *et al*. (2005). *Prevalence of multimorbidity among adults seen in family practice.* Annals of Family Medicine **3(3)**, 223-228.

[5] NICE Medicines and Prescribing Centre (2015). *Medicines Optimisation: The Safe and Effective Use of Medicines to Enable the Best Possible Outcomes; NICE Guideline 5*; https://www.nice.org.uk/guidance/ng5/resources/medicines-optimisation-thesafe-and-effective-use-of-medicines-to-enable-the-best-possible-outcomes-pdf-51041805253

[6] Kongkaew C, *et al.* (2008). *Hospital admissions associated with adverse drug reactions: A systematic review of prospective observational studies.* Annals of Pharmacotherapy **42(7-8)**, 1017-1025.

[7] Academy of Medical Sciences (2018). *Multimorbidity: a priority for global health research.* https://acmedsci.ac.uk/file-download/82222577

[8] Academy of Medical Sciences (2020). *Cross-funder multimorbidity research framework.* https://acmedsci.ac.uk/file-download/50613213

themes derived from the research priorities within the 2020 framework were identified as areas for further discussion:

1. Adopting data-driven approaches to identify true disease clusters, help inform research efforts, prioritise the most promising areas and understand patient populations to ensure research remains relevant.
2. Understanding the biological mechanisms that link disease clusters to reveal new opportunities for drug development, novel drug targets, and to treat multiple conditions with single pathways and reduce polypharmacy.
3. Incorporating more patients with MLTC into clinical trials to ensure that treatments are proven effective and safe in these patients, who are the population most likely to be seen by clinicians in practice.

These themes, while not encompassing all aspects of research into MLTC, each represent key areas where advances would enable the timely development of better interventions. In addition to these, the research system must of course consider other areas, including elements of behavioural and social sciences such as self-management, quality of life, patient empowerment and social care, the intersection between physical health and mental health and the implications of this, and the importance of prediction and prevention in stopping MLTC from occuring in the first place.

On 19 and 22 October 2020, the Academy of Medical Sciences, the MRC and the NIHR held a joint workshop to examine the respective opportunities and challenges for each of these priorities amongst a cross-sector audience drawn from academia, industry, the NHS and wider life sciences sector.

Patient perspectives on multiple long-term conditions

The term MLTC covers diverse combinations of health conditions. Dr Cheryl Gowar and Dr Jennifer Bostock discussed their experiences living with MLTC and provided their perspective on how making research and health systems more suitable for people with MLTC could bring huge benefits to patients.

Living with and managing MLTC can become a 'full time job' for the patient, including factors such as appointment burden, travel to specialist clinics, medication and test result management, staying informed about developments in the disease areas and self-advocacy. The frustration of being asked the same questions by different medical practitioners was also highlighted. While some experiences may be unavoidable, it was noted that a health and social care system that considered a patient holistically – and was truly patient-centred – could significantly reduce these burdens.

"As soon as I enter hospital, my conditions are dealt with in isolation, with no recognition that they are bound together in a person."

Dr Jennifer Bostock, patient representative

Clinical decision making done in isolation can lead to treatment and advice that is contradictory, not responsive to multiple needs or even conflicts with other issues. This can cause patients to lose confidence, leading some to drop out of care or treatment. Dr Bostock noted that this was particularly significant in hospitals and that there was a need for medical generalists (similar to the role of geriatricians for older people) and care-coordinators who can see the medical needs of a patient in a holistic context. The latter has parallels with rare diseases patients who have an NHS care co-ordinator that ensures coordination and continuity of care.[9] Research into polypharmacy, contraindications, and adverse reactions was also considered paramount for improving prescribing practices.

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[9] NHS England (2018). *Implementation Plan for the UK Strategy for Rare Diseases.* https://www.england.nhs.uk/wp-content/uploads/2018/01/implementation-plan-uk-strategy-for-rare-diseases.pdf

"Research on multiple long-term conditions could instil the principle of understanding the whole person. If research is integrated, treatment and care is more likely to be integrated and patients will have more confidence in their treatment."

Dr Cheryl Gowar, patient representative

Scientific research, much like the health and social care system, happens in silos. A more integrated research system could lead to the development of treatments more relevant for patients with MLTC and thus improve care. Dr Gowar emphasised inclusion as a key principle for research. This includes seeing the patient holistically, considering both physical and mental health conditions together, as well as other contributory factors such as poverty, homelessness and migration status. MLTC research shouldn't be confined to the ageing population – it can often also affect younger patients.

The importance, but current lack of, patient involvement in setting and prioritising research questions was highlighted. This involves researchers relinquishing some control over research priorities, but opens up a rich and vital source of information – the patient experience. Patient involvement for those with MLTC may be more complicated due to a diversity of experiences, but remains essential to ensure progress in responding to the needs of patients. It was emphasised that many patients with MLTC are enthusiastic about being involved in trials, but these are nearly always 'single issue' trials, overlooking the complexity of the MLTC patient experience and hindering participation. To address this, broadening the inclusion of research subjects with MLTC in single issue trials and building in advice from local patient and public involvement experts were suggested (see Annex I for an overview of moving beyond single targets for single diseases provided by Dr Sheuli Porkess, Executive Director of Research, Medical and Innovation at the Association of the British Pharmaceutical Industry). Finally, the communication of research is crucial. Translating and disseminating findings in an accessible way to the public enables patients to be informed about and to participate in their own care.

Multiple long-term condition research priorities

The Academy's 2018 report, *Multimorbidity: a priority for global health research*, highlighted a number of research priorities for the MLTC field.[10] The subsequent cross-funder framework set out to help co-ordinate efforts and initiatives in MLTC research, and to highlight opportunities for funders to work together on areas of common interest or benefit.[11] To address the research priorities outlined in these two documents, there is a need to bring together and build relationships across different sectors to discuss the key opportunities and foreseeable challenges of embedding an MLTC approach into research programmes. There is also a need to facilitate a unified mechanism to accelerate research that will lead to better interventions for patients. Discussions at the workshop focussed on three of the research priorities identified in our reports, each of which is considered in turn below.

Theme 1: Data-driven approaches at the heart of understanding multiple long-term conditions – harnessing existing assets and creating new ones

Making the most of existing academic and industry data sources and infrastructure

Participants discussed how datasets are not always widely known about or easily

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[10] https://acmedsci.ac.uk/policy/policy-projects/multimorbidity
[11] Academy of Medical Sciences (2020). *Cross-funder multimorbidity research framework.* https://acmedsci.ac.uk/file-download/50613213

accessible to researchers (see Annex I for an overview of data-driven approaches to understanding MLTC provided by Professor Ronan Lyons, Clinical Professor of Public Health at Swansea University at the workshop). Those responsible for data sources – including real-world, cohort, trials, and experimental data – should work to raise awareness of available datasets and support researchers in accessing them, especially where they may not have experience of navigating the governance required to access them.

Linkage of existing datasets provides unique opportunities to undertand MLTC, but this can be practically challenging. It was suggested that allowing and encouraging the linkage of datasets – contingent on properly managed data and secure environments – should be seen as the standard default, rather than the current system where it is an additional step with further administrative burden. Once linked and accessible, machine learning approaches might be needed to unpick the complexity of these datasets, which can also accelerate their interrogation. It will be important that findings from data-driven approaches are validated through other means. Once clear disease clusters are identified and the biological and social meaningfulness of the clusters are established, proactive and early discussions with industry should be held to identify opportunities for novel treatment development.

UK cohorts for MLTC research should be maintained and opportunities to combine data sources encouraged, given that combining datasets allows multifactorial analysis which can be advantageous to wider MLTC research. A multi-funder approach could be considered to support cohorts to provide access for research that focuses on MLTC rather than single diseases or outcomes.

New data sources and analytic tools are required

Participants proposed new data sources and analytical tools that could drive forward data approaches to MLTC research. These included:
- Incorporating more molecular data into datasets that include populations with MLTC, which would provide new insights into concurrent conditions.
- Ensuring that databases and cohorts are longitudinal where possible, acknowledging that this requires longer term funding commitments than usually available. Ideally, these cohorts would track people before they suffer significant health conditions and through the development of MLTC.
- Understanding and defining the biological and environmental factors that influence outcomes, both at the level of the patient and the health service, which would provide insights into mechanistic research.
- Including geographical and place-based data in cohort studies, as these influence disease aetiology. Factors affected by geography could include environmental exposure, access to green space, access to healthy food, and how health and social care works in terms of caring for people with MLTC.
- Linking interventions in MLTC to social outcomes, which could help to demonstrate their efficacy and effectiveness.
- Patient and public involvement and engagement (PPIE) guiding disease clustering and data approaches. Research is needed to determine what outcomes, and therefore data, are important for patients and their quality of life.
- Exploring greater use of primary care data through the use of natural language processing to make sense of free text records that lack the standardisation and coding of more formal data collection. Clear data about treatment pathways and patients' progression to multiple conditions would be very valuable to understanding MLTC.

Data from other relevant services, such as social care and community health services, would provide useful insights to longitudinal health.

- Undiagnosed (or under-diagnosed) conditions, which are a source of poor-quality data. Participants asked whether a data platform may be able to actively look for conditions over time, for example through annual examinations for a cross-section of the population. This would assist in capturing the full effects of MLTC.

Infrastructure and research ecosystem changes needed to streamline disease clustering research and link it to commercial R&D

Standards and definitions were a key topic of discussion for participants. The research community has yet to define the terms associated with MLTC, which may impair standardisation across datasets and wider research projects. The benefits of having national agreements on a standard data model with standardised data curation and data access management, were emphasised by participants. As noted previously, data linkage could be set as the default rather than the exception within this model. However, it would be critical to ensure that data use is transparent with a complete audit trail; PPIE would be essential to ensure any new system is acceptable to the public.

Promoting team science, open science and transparency is important for a productive research ecosystem.[12] Promoting open access and sharing code and analysis could help move the field forward; although often a requirement from funders, some suggested it was a 'tick-box exercise'.

International collaboration will be essential to providing new datasets and insights into diverse and larger populations. As such, considering the international landscape and how researchers can work to harmonise and interpret data at scale beyond the UK is crucial. This will need to be supported by a system that provides the research community with the scale and rapidity that is needed to answer important research questions.

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[12] Academy of Medical Sciences (2016). *Improving recognition of team science contributions in biomedical research careers.* https://acmedsci.ac.uk/file-download/6924621

Next steps for data-driven approaches to MLTC research

A number of priority areas were highlighted by participants:

1. **Maximising the use of the UK's many rich data sources.** Such datasets are not always widely known about or easily accessible to researchers. The community should work to **raise awareness of available datasets and support researchers in accessing them**.

2. **Embracing distributed team science at scale**: utilising and extending existing resources and networks to simplify the provision of analytical access to real-world, cohort, trials and experimental data (both public and commercial) for UK and international teams.

3. The need for **deep phenotyping in longitudinal cohorts**, considering trajectory and severity of disease and defining factors that influence outcomes both at the level of the individual patient and the health service.

4. **Building and maintaining cohorts and linked datasets suitable for MLTC research** – the combined value of which is far greater than the sum of the parts. A multi-funder approach should be considered to help create and support cohorts that will provide access for research that focuses on MLTC rather than single diseases or outcomes.

5. **Developing understanding and encouraging collaboration between data scientists and clinical researchers, and service users and patient communities.** These communities need to come together to develop their understanding of MLTC and consider the meaningfulness of disease clusters and the research opportunities they present.

Theme 2: How understanding biological pathways is providing new opportunities to develop interventions

Identifying new pathways that link multiple conditions

MLTC research is a large and diverse field. Participants suggested that researchers need to focus efforts on specific research questions that address known disease clusters or promising mechanistic links (see Annex I for an overview of the importance of understanding the biological pathways underlying MLTC provided by Professor Janet Lord FMedSci, Professor of Immune Cell Biology, University of Birmingham at the workshop). As mentioned previously, phenotyping of longitudinal cohorts was highlighted as essential to uncover the biological mechanisms that underlie linked conditions to focus research questions. It was suggested that phenotyping needs to include the trajectory and severity of disease, and treatment pathways. Prospective cohorts could augment these data by tracking patients from their first condition to the development of multiple conditions.

Inflammation, infection and senescence were considered to be among core processes underpinning the development or exacerbation of MLTC. However, the complexity of these mechanisms was highlighted; targets in the pathway may change dependent on, for example, the organ of origin. Beyond the inflammatory, infection and cellular senescence pathways, AI approaches could be utilised to identify new pathways underpinning multiple conditions.

While most people with MLTC are older, the mechanisms of disease in younger people with MLTC may be different. These should be differentiated in research to ensure a life course perspective is included and age-specific multimorbidity is explored.

Key evidence sources and gaps to identify novel drug targets

Research into the mechanisms underlying MLTC and novel drug targets will require the effective use of both new and existing evidence sources. These include both new and existing cohorts and big data repositories, and programmes in the human experimental medicine space. The importance of reverse translation approaches – taking insights from clinical research and practice, and from *in vivo* animal models to inform research into novel treatments – was also highlighted.

One of the key challenges in addressing multimorbidity identified at the meeting was the lack of appropriate experimental animal models, which are yet to be developed beyond inducing conditions in young, healthy animals. Generating animal models that recapitulate more complex biology with multiple indications would be invaluable to understanding the biology of MLTC. Fly and fish models may allow the impact of age to be factored in more rapidly and at a lower cost than is possible with mouse models.

New technologies, such as 'multi-omics' approaches, organoids and induced-pluripotent stem cells, provide new opportunities for research and for exploring mechanistic links of disease. By triangulating multiple evidence sources – from cellular models, *ex vivo* work, epidemiology, multi-omics, animal models, AI and modelling – new targets, biomarkers

and endpoints can be identified that are more relevant and have a higher likelihood of supporting successful therapeutic development.

Stimulating MLTC approaches in drug discovery programmes

Encouraging collaboration across academia and industry was considered to be a critical step towards the development of novel MLTC drug discovery programmes. The most successful collaborations start at initial project conception and map the clinical development path to ensure appropriate endpoints are used in trials and to give 'line of sight' for adoption. Defining appropriate endpoints that are relevant for MLTC, rather than individual diseases, would need discussion with patients, clinicians and regulators, and a recalibration of the field to redefine these over time.

Participants noted that for industry to be fully engaged and involved, there needs to be support in de-risking prospective drug targets for multiple conditions. These novel approaches are currently high risk, so the wider community, including academia, can support industry by carrying out vital *ex vivo*, *in vivo* and epidemiology research.

Next steps for mechanistic MLTC research

A number of priority areas were highlighted by participants:
1. The need to **continue to develop translational technologies that will support mechanistic research,** such as animal models and organoids, and to better engage fundamental and drug discovery researchers in MLTC research.
2. The need to **triangulate multiple evidence sources to de-risk novel drug targets for industry** as targeting multiple diseases is currently very high risk. Good evidence would

involve triangulation of data from *ex vivo*, epidemiology and animal models. Greater use of AI and modelling may help to confirm or identify new targets.

3. **Key evidence sources can be used for developing hypotheses and facilitating a reverse translation approach,** including existing cohorts and big data repositories, and programmes in the human experimental medicine space.

4. The **importance of collaboration with industry** was strongly highlighted. In particular, working collaboratively on drug targets rather than specific diseases to develop treatments/drugs for MLTC that target common pathways.

5. The **importance of defining the clinical development pathways early on**, so that appropriate endpoints are used (e.g. in trials) that are relevant for MLTC rather than individual diseases. Discussion with patients, clinicians and regulators and a recalibration of the field would be needed to redefine these over time.

Theme 3: How do we facilitate clinical trials that are inclusive of patients with MLTC?

Key challenges for incorporating patients with MLTC into clinical trials

Ensuring inclusion of people with MLTC in clinical trials is more complex than just widening inclusion criteria, as people with MLTC may have additional needs or concerns that need to be addressed (see Annex I for an overview of the challenges and opportunities for including more patients with MLTC in clinical trials provided by Professor Deborah Ashby OBE FMedSci, Director of the School of Public Health, Imperial College London at the workshop). As such, researchers need to have a robust recruitment strategy when planning a trial where participants may have MLTC.

In addition, groups who are already underrepresented in clinical trials are often also those at increased risk of developing MLTC. These groups could include women, ethnic minority groups, and those from disadvantaged socioeconomic backgrounds. To increase representation among these groups, innovative recruitment strategies might be required.

Participants also noted that ensuring that clinical trials for MLTC can achieve statistical power and effectively recruit participants will require new commitments from funders and researchers to meet the increased time resources and cost. Furthermore, clinicians will need support to recognise that they can recruit more complex patient groups into

appropriate trials given that this would be a marked change from current recruitment criteria.

Tools and approaches for incorporating patients with complex needs into trials

Researchers

Widening participation in clinical trials requires researchers, funders, clinicians and patient-facing organisations to come together to cut across sectors, clinical specialties and therapy areas. Researchers need to be aware of and overcome barriers to recruiting people with MLTC into trials. This requires commitment, time and resources from the whole research community, including funders. Suggestions from participants included:

- Sharing knowledge of exemplar projects that demonstrate how these types of trials can be designed and delivered, which would serve as valuable learning points for the research community.
- Requiring trials to collect data on patient diversity and characteristics (e.g. proportion of patients from underserved backgrounds, those with MLTC) as part of the study, which may drive a change in practice.
- Building trust and co-production, which will be integral to expanding recruitment. This would include researchers working more closely with community and faith leaders. There is a need to understand and help overcome barriers to inclusion and raise awareness of the benefits of participating in research. Ensuring plain language is used in patient information sheets and co-producing these with patients is an essential step towards ensuring trust.
- Ensuring trials are easy and convenient to take part in, for example, by accommodating participants' other responsibilities, such as childcare, and the burdens associated with taking part in a trial, such as transport.
- Better understanding the patterns of disease clusters to enable researchers to better understand the real-world distribution, impact and unmet need of MLTC to ensure that trial designs, the research questions they attempt to answer, and the participants they involve are representative and relevant.
- Capturing and reporting comorbidities in a standardised way to allow data from multiple trials to be compared and scrutinised. This capturing needs to take place in both research delivery systems (e.g. the NIHR CRN) and in trials reports.

A recurring theme in discussions was the need for patients to be at the centre of efforts to design trials, including patient reported outcome measures, recruitment and delivery strategies. Simpler, more focussed and inclusive trials are needed, delivered in ways that are convenient to patients. Trials with PPIE embedded early on can lead to the development of trials that are both accessible and attractive to patient groups, making it easier to recruit and retain participants. Researchers should co-produce trials to make them more relevant to what matters to patients, making the trials more likely to benefit patients.

Regulators

Participants suggested that there is a misconceived view that regulators may not be accepting of new trial designs. To overcome this, early dialogue with regulators can support those designing and sponsoring trials involving patients with MLTC or for drugs that target multiple conditions. There was a clear appetite from regulators for researchers to proactively approach them with innovative ideas for MLTC research and work with them to ensure the appropriate regulation for MLTC research. There are currently no known frameworks to support trials that are inclusive of patients with MLTC. However, industry and other trial sponsors are reliant on the regulation and guidelines

provided by regulatory bodies, HTA bodies and service commissioners. It was suggested that there is a need to establish what practical steps can be taken forward, and explicit guidance from regulators could support these conversations. This could be an opportunity for UK funders, researchers and regulators to work together to design relevant guidelines for MLTC research. Participants suggested that regulators such as the MHRA could produce 'points to consider' guidance to support clinical trials that are inclusive of patients with MLTC.

Funders
Funders have a critical role in supporting and stimulating trials that break paradigms through using adaptive designs and innovative multi-sector and multi-disciplinary collaborations. Consideration needs to be given to how funders encourage researchers to recruit more complex patients into trials, removing barriers to ensure these types of grant applications are appropriately assessed and allowing for increased potential costs and time to recruit. Commissioning panels will need to be supported to understand and appreciate new models, which may be more technically complex.

Opportunities for trials involving patients with MLTC

It was suggested that one opportunity for making trials more representative of populations is nesting experimental paradigms in established well-characterised cohorts, such as the 'Trials within Cohorts (TwiCs)' trial design.[13] Participants also suggested that trials could focus on symptoms that patients consider a priority, for example fatigue and pain, rather than disease type or aetiology. It was noted that many of these approaches are possible and accepted by regulators, but there is a lack of awareness of these opportunities amongst researchers or incentives to encourage their use.

The COVID-19 pandemic has shown that clinical trial applications can be reviewed at speed. It was agreed that the best elements of these 'fast-track' processes should be retained post-pandemic. In addition, COVID-19 clinical trials have shown tremendous success in using technology to recruit and enable patients to participate from home, which could be used as an exemplar for future studies. However, this approach may also lead to exclusion of those who do not have access to technology, for example smart phones.

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[13] https://www.twics.global/

Next steps for clinical trials that are inclusive of patients with MLTC

A number of priority areas were highlighted by participants:

1. The need to **put patients back at the centre of trial design and delivery** – simpler trials that are more focussed and inclusive are needed, delivered in ways that are convenient to patients.

2. **Exclusion of patients with MLTC is closely related to other forms of inequity in access to trials** - populations who get excluded for socio-economic reasons are often those with MLTC. Solutions to engender trust and co-production, with strong PPIE, are required.

3. The need to **capture and report comorbidities in a standard way**, both in research delivery systems and trial reports.

4. The **need to bring stakeholders and diverse clinical networks together** to cut across silos, developing 'exemplar projects' as a starting point.

5. **Funders have a critical role to play to stimulate trials that are not just single disease-focussed.** Given the pressures that some funders are facing because of the COVID-19 pandemic, innovative collaborations between funders could be timely.

6. **The importance of speaking to regulators early** to agree on designs for MLTC trials and possibly to define exemplar protocols. The **MHRA could develop a 'points to consider' document for MLTC trials**, which would act as the basis for discussions between regulators and sponsors about how MLTC are handled in regulatory submissions.

How do we embed MLTC into research pathways across the life sciences sector?

Drawing together the discussions of the three MLTC research priorities defined in the previous chapter, participants considered the system-level considerations and priorities for facilitating MLTC research. They also explored mechanisms to incentivise and accelerate the development of interventions for patients with MLTC in the near term.

Changes to current clinical pathways and healthcare delivery to meet the needs of patients with MLTC

Health services research and policy-focused research to evaluate the impact of interventions or changes to service delivery on the quality of care provided for people with MLTC could help tackle some of the everyday issues highlighted by the patient representatives, such as disjointed care and lack of co-ordination between different specialist teams. For example, findings from disease clustering research could inform the design of patient care pathways, and subsequently by clinicians and patients in shared decision making about treatments. Mapping patient journeys, from symptoms to diagnosis and treatment, could help identify better touch points or missed opportunities to meaningfully intervene earlier. Understanding the trajectories of disease could allow intervention at key points, preventing or slowing the development of new concurrent health conditions.

The siloing of disease specialists within the health and social care system was highlighted by participants as an issue, in particular the separation of physical and mental health conditions. The need for generalists, as well as specialists, in hospitals was also discussed, including how clinical staff could integrate specialist knowledge and health outcomes about comorbidities with other factors to treat patients holistically.

Putting patients at the heart of MLTC research and trials

PPIE is essential to ensuring research outputs are relevant and address patient needs and priorities. PPIE is an integral component across all areas of the translational pathway, from setting research priorities and determining standards, to trial design and research communication. Further work is needed to consider how to best gather

information about what is important for patients and how this can be built into MLTC research programmes. If patient needs and research priorities are not aligned, MLTC targets and interventions may not be relevant to the core problems that need to be addressed.

Patient-centred research needs to: understand the experience of patients with MLTC, including the time and economic burden; consider patients holistically; and ensure their needs, priorities and preferences are heard and acted upon. For example, embedded qualitative analysis in clinical trials for drugs (as is often seen in trials of complex interventions) could add valuable data about patients' real-world experiences. As mentioned in Theme 3, inclusion is central to effective PPIE and explicit consideration of underrepresented groups is required to ensure research is relevant to the target patient population.

Creating a shared language through a common set of definitions and standards

MLTC research requires the collaboration of those working in different disease areas and fields. The need to move towards a standardised definition and classification system for multimorbidity was previously highlighted in the Academy's 2018 multimorbidity working group report.[14] Standardisation was a common thread running through all three research themes, including: definitions for multimorbidity and MLTC clusters; standard data models; consistent coding of data; and standardising the reporting of adverse drug reactions and multimorbidity across clinical trials. A common set of definitions, reporting systems and standards would help establish a shared language between researchers and clinicians across the life sciences sector, improving communication and collaboration.

However, there was also recognition of the power of allowing patients to report their own symptoms, as has been demonstrated by the COVID-19 symptoms app and online platforms such as 'PatientsLikeMe'.[15] A blended approach with patients as key partners in developing standardisations could be a potential solution - as has been seen in the SONG (Standardised Outcomes in Nephrology) initiative.[16]

Developing skills and training for MLTC researchers

A paradigm shift from single disease to MLTC research and treatments will also require a parallel shift in skills for both clinical and non-clinical researchers. Participants felt there was a need to assess the skills gaps and training needs in MLTC research. This was highlighted across the three research themes; for example, for data-driven approaches, data scientists with an understanding of the biological meaningfulness of disease clusters will be needed.

More widely, it was suggested that researchers need to develop their understanding of multimorbidity, its implications for their research area and how their research complements the wider MLTC research landscape. Improving and enabling better

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[14] Academy of Medical Sciences (2018). *Multimorbidity: a priority for global health research* https://acmedsci.ac.uk/file-download/82222577
[15] Frost J & Massagli M (2009*). PatientsLikeMe the case for a data-centered patient community and how ALS patients use the community to inform treatment decisions and manage pulmonary health.* Chron Respir Dis **6(4)**, 225-229.
[16] https://songinitiative.org/

communication between different fields was considered essential to productive research collaborations. Participants acknowledged the importance of these skills to enable engagement with commercial R&D.

Bringing together single disease and other national research funders to drive the MLTC research agenda

The role of charities and other research funders in driving the MLTC research agenda across the sector was discussed. Participants noted the importance of single disease charities and organisations acknowledging the importance of MLTC and working together to promote work in this field. Funders can also provide clarity and focus on particular disease clusters. The Academy, MRC, NIHR and Wellcome have developed a cross-funder MLTC research framework which aims to co-ordinate MLTC research efforts and initiatives across these organisations.[17] The NIHR has also developed an MLTC Strategic Framework outlining steps to create a common understanding of MLTC across its research community.[18]

A number of charities are already working in this area, including, for example, Kidney Research UK and Versus Arthritis. The Advanced Pain Discovery Platform is an example of co-funding that brings together different disease types to explore mechanisms underlying a common symptom and ways to improve treatments.[19] The Richmond Group taskforce is another of example of coordination of single disease charities' work on MLTC, which has produced a range of patient-centred reports and resources.[20]

Societies and publishers can also play a role in promoting MLTC research through cross-disciplinary meetings, conferences and publications to attract researchers and foster discussions across different networks, sectors and disciplines.

Supporting cross-sector collaboration and knowledge exchange through public-private partnerships

Platforms and infrastructure to enable mutually productive cross-sector collaboration and knowledge exchange were heavily emphasised. There are a number of initiatives aiming to improve industry and academic partnerships that were highlighted by participants, including:

- The 'Innovative Therapeutics for Ageing Consortium' (iTAC), which was formed to accelerate the discovery and development of therapeutics for ageing, refocus drug development towards tackling core ageing processes, and better meet the needs of those with MLTC.[21] This public-private partnership is a drug discovery and development platform, sharing the efforts and assets of different partners to drive forward drug development and acting as an enabling translational pathway for academia and industry.

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[17] Academy of Medical Sciences (2020). *Cross-funder multimorbidity research framework.* https://acmedsci.ac.uk/file-download/50613213
[18] https://www.nihr.ac.uk/documents/research-on-multiple-long-term-conditions-multimorbidity-mltc-m/24639
[19] https://mrc.ukri.org/research/initiatives/advanced-pain-discovery-platform-apdp/
[20] https://richmondgroupofcharities.org.uk/taskforce-multiple-conditions
[21] Ford G, *et al.* (2019). *Organizational innovation for developing new medicines that target aging and age-related conditions.* J Gerontol A Biol Sci Med Sci **75(1)**, 87-88.

- Dementias Platform UK (DPUK), which is a public-private partnership funded by the MRC, providing researchers with rapid online access to cohort data and enabling collaboration with industry in a pre-competitive environment.
- The AstraZeneca OpenInnovation platform, which aims to facilitate research collaborations with academia, industry, non-governmental organisations and governments via a number of open innovation programmes, including providing access to preclinical data and patient-ready compounds.[22]

Participants suggested such platforms should be promoted as they are integral to enable MLTC research.

Funding and highlighting exemplars of MLTC studies that demonstrate success and feasibility

Proof-of-concept trials, demonstrating the ability to treat MLTC with drugs targeting common pathways, or to treat symptoms common across MLTC, were identified as an important enabler for larger or more complex studies. Such trials, with designs accepted by regulators and patients, would be an important step in encouraging industry to adopt an MLTC approach. A programme of proof-of-concept studies could provide a systematic way to demonstrate that there are opportunities to make positive interventions that affect multiple conditions simultaneously.

Moving towards preventing the development of MLTC

Many MLTC have common modifiable risk factors. A number of participants noted that current MLTC research is heavily treatment focused and not sufficiently prevention focused. It was suggested that more could be done in the prevention space, leading to longer-term health benefits for society and better use of healthcare resources. Researchers should consider how to integrate prevention or risk reduction into MLTC research and trials, identifying where best to intervene across the patient journey to prevent the subsequent development of MLTC. A coherent approach to prevention, aiming to delay or prevent the development of MLTC, would significantly improve both the overall quality of life, as well as the length of life, of patients.

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[22] https://openinnovation.astrazeneca.com

Conclusion

The meeting co-Chairs closed the workshop by reflecting on some of the key next steps for the community. They emphasised:

- The vital need for cross-sector knowledge exchange and collaboration given the varied specialisms and therapy areas within MLTC research and healthcare delivery. By better linking up the research priorities of basic scientists, population scientists, epidemiologists, drug discovery and translational scientists, new discoveries can be quickly seized upon to accelerate the development of promising treatments.
- Three pillars of support and infrastructure from the wider community can help harness these opportunities: longitudinal cohorts, exemplar proof-of-concept clinical trials and the co-production of clinical endpoints that are meaningful to patients.
- None of this can be achieved without a workforce that has the necessary skills, experience and appetite to work across boundaries and build collaborations. A culture of collaboration and team science will give rise to new opportunities to understand MLTC and develop new interventions.

Ultimately, progression in the field will rely on investment in people, infrastructure and innovative techniques in a way that maximises the chances of uncovering new and tractable answers to some of the biggest questions facing MLTC research.

Annex I – Presentations

This annex provides summaries of the speakers' presentations that were given during the workshop, which provided important context to facilitate the discussions that took place.

Moving beyond one target for one disease: What does industry need to incorporate multimorbidity approaches?

Much like academic research, the pharmaceutical industry has a paradigm of developing medicines for patients with a single disease. Dr Sheuli Porkess, Executive Director of Research, Medical and Innovation at the Association of the British Pharmaceutical Industry (ABPI) discussed what is needed to shift this paradigm to support industry uptake of the opportunities of MLTC research.

Dr Porkess described the recently formed ABPI-led industry stakeholder group on multimorbidity, established to tackle the issue of increasing numbers of patients with multiple co-existing diseases. For example, in chronic obstructive pulmonary disease (COPD), an area of strong interest and activity for the pharmaceutical industry, only 6% of patients have COPD as their sole condition, raising the question as to how industry could develop medicines for the 94% of patients with co-occurring conditions.[23]

The action group includes ABPI members, representatives from Birmingham Health Partners, the Academic Health Science Network, British Pharmacological Society and Academy of Medical Sciences. The group is exploring the challenges facing the pharmaceutical industry when considering the research, development and usage of medicines for patients with MLTC, in a system built upon the 'single disease' paradigm.

There are a number of challenges and questions when considering how to move from single disease drug development to an MLTC approach. These can be considered across the various stages of drug development:
- *Discovery & Target Identification*: What are the biological targets for MLTC?
- *Research*: What is the Target Product Profile? Is a product designed for one disease that may be used in another, or is it specifically developed to target a cluster of diseases?

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[23] Mapel DW, *et al.* (2000). *Health care utilization in chronic obstructive pulmonary disease: a case-control study in a health maintenance organization*. Arch Intern Med **160**, 2653–2658.

- *Development*: What milestones does a product need to meet during pre-clinical and clinical development? How do we ensure the clinical population is representative of the intended patient population?
- *Licensing & Reimbursement*: What are the regulatory standards? What endpoints need to be met? What will be needed for reimbursement?
- *Clinical Use*: How will new products be used in practice? What support is needed to ensure appropriate prescribing?

Dr Porkess highlighted that this would require a shift in thinking and the development of a whole new skill set across the drug development pathway.

Multiple long-term conditions and COVID-19: urgent questions and priorities

Infectious diseases can sometimes be overlooked in discussions on MLTC, despite being a significant contributor to the global burden of MLTC. The COVID-19 pandemic has brought into clear focus the impact of infectious diseases, especially on those with pre-existing conditions. Professor Kamlesh Khunti FMedSci, Professor of Primary Care Diabetes and Vascular Medicine at the University of Leicester, and Professor Alan Silman FMedSci, Professor of Musculoskeletal Health at the University of Oxford, discussed the urgent questions and priorities for MTLC and COVID-19, including risks and long-term challenges facing patients with MLTC.

COVID-19 and MLTC can be seen as a triple-edged problem, as those with MLTC are more susceptible to severe COVID-19; infection can lead to the development of post-COVID syndromes (commonly referred to as 'long COVID'), including further MLTC; and disruption to routine care can result in poorer outcomes in the long term for patients with MLTC.

The Academy's 2018 multimorbidity report highlighted the challenges of studying MLTC. This included understanding which disease clusters are important, how to understand and take into account different levels of disease severity, and how comorbid diseases interact with other factors such as gender, age, ethnicity, obesity, among others.[24] These difficulties are exacerbated when considering the impacts of COVID-19 on patients with MLTC, due to the need for accurate real-time information. New datasets are needed to understand how the virus spreads, who is most at risk and the impact on health care services. Professor Khunti described an overall lack of good quality publications on MLTC and COVID-19 related outcomes. Furthermore, COVID-19 has had a disproportionate impact on ethnic minority groups, but there is very little associated data on ethnicity and MLTC.

Professor Silman described the urgent need to consider how MLTC may impact the likelihood of transmissibility and risk of severe COVID-19 infection. Data from UK

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[24] Academy of Medical Sciences (2018). *Multimorbidity: a priority for global health research* https://acmedsci.ac.uk/file-download/82222577

Biobank has shown that those with cardiometabolic long-term conditions were 1.7 times more likely to test positive for COVID-19, irrespective of symptomatic disease. Those with MLTC and additional factors, such as non-white ethnicity, obesity and socioeconomic disadvantage, were also at heightened risk of COVID-19.[25] Obesity is associated with conditions such as diabetes, cardiovascular disease and COPD. Other studies show an association between testing positive for COVID-19 and higher body mass index (BMI).[26] The association between obesity and severe outcomes from COVID-19 is increased in ethnic minority groups, suggesting that the combination of obesity and ethnic minority status may place individuals at a high risk of contracting COVID-19.[27]

It has now been well-described that the risk of dying from COVID-19 is not only related to age, but also to the number of underlying conditions.[28] It has been estimated that the risk of hospitalization, intensive care unit admission and mortality for COVID-19 is approximately two fold higher for every additional health condition a patient has.[29] Meta-analysis has shown that cardio-metabolic diseases are driving the increased risk of severe COVID-19 (defined as hospitalisation or mortality), with hypertension, diabetes and cardiovascular disease being the most prevalent co-morbidities in people admitted to hospital with COVID-19.[30]

It was first thought that COVID-19 was a short, relatively mild illness in most people, but as the pandemic continues, an increasing number of people have been suffering from 'long COVID'. A recent study estimated that one in 20 people are likely to suffer from COVID-19 symptoms lasting more than 8 weeks.[31] Long COVID is associated with a vast range of symptoms, including respiratory symptoms such as breathlessness and multi-system symptoms such as fatigue, heart palpitations, anxiety, depression and joint or muscle pain. Thus, long COVID may lead to an increase in patients with MLTC. While it is not known whether having MLTC prior to SARS-COV-2 infection increases the likelihood of long COVID, Professor Silman indicated that prior comorbidities or prior indices of poor health status (including cardiometabolic, musculoskeletal and psychological health) seem to be associated with subsequent longer term poor health following COVID-19.

Both Professor Khunti and Professor Silman emphasised the importance of mental health, which is known to affect management of chronic disease, adherence to medications and physical activity. The Academy and MQ have endorsed a number of mental health and neuroscience research priorities exploring the psychological, social and neuroscience impacts of COVID-19.[32]

Finally, the COVID-19 pandemic has significantly impacted health and social care delivery. The disruption in routine care for patients with chronic diseases will lead to

[25] McQueenie R, *et al.* (2020). *Multimorbidity, polypharmacy, and COVID-19 infection within the UK Biobank cohort.* PLOS ONE; e0238091

[26] Yates T, *et al.* (2020). *Obesity and risk of COVID-19: analysis of UK biobank* Primary Care Diabetes **14(5)**, 566-567.

[27] Razieh C, *et al.* (2020). *Body mass index and the risk of COVID-19 across ethnic groups: Analysis of UK Biobank* Diab Metab **22(10)**, 1953-1954.

[28] Baerjee A, *et al.* (2020). *Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study* The Lancet **395(10238)**, 1715-1725.

[29] Froes MT, *et al.* (2020). *Comparison of Multimorbidity in COVID-19 infected and general population in Portugal* medRxiv preprint

[30] Singh AK, *et al.* (2020). *Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis* Diabetes Obes Metab, Epub 2020 Jul 16.

[31] Sudre C, *et al.* (2021). *Attributes and predictors of long COVID* Nature Medicine

[32] Holmes E, *et al.* (2020). *Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science* The Lancet Psychiatry **7(6)**, 547-560.

worse outcomes in the long-term. A global survey of views from healthcare professionals found that routine care for diabetes, COPD, hypertension, heart disease, asthma, depression and cancer – conditions which are commonly concurrent with other MLTC – were considered to be the most impacted by COVID-19.[33] Professor Khunti emphasised the urgent need to start thinking about clinical care and chronic disease management for those at high risk during the disruption. There are a number of studies planned or ongoing such as the International Severe Acute Respiratory and Emerging Infection Consortium, British Health Foundation-Health Data Research (HDR) UK consortium, openSAFELY, and Post-Hospitalisation COVID-19 Study (PHOSP-COVID).[34,35,36,37]

Data-driven approaches to understanding MLTC

Data-driven approaches are providing new opportunities for MLTC research. Professor Ronan Lyons, Clinical Professor of Public Health at Swansea University, discussed the UK data landscape.

In the UK, there are two principal categories of data assets that contribute to the agenda on data-driven approaches to disease clustering: longitudinal studies (traditional cohorts) and the use of routine data (electronic cohorts). Both categories of data are required to answer the wide-ranging questions on disease clusters, mechanisms, trajectories, and patient and population impacts.

Within traditional recruited cohorts, the UK has 2.5 million participants – with some including genomic, multi-omic and imaging data. Important studies and initiatives for multiple long-term conditions include: UK Biobank, the Avon Longitudinal Study of Parents and Children, Lothian Birth Cohorts 1921/1936, MRC Dementias Platform UK and Population Research UK. There is no single set of data that can be used for all research questions, with each dataset having advantages and disadvantages. For example, UK Biobank contains an incredible depth of data on 500,000 participants to study disease associations and mechanisms. However, the bias towards healthy volunteers means there are substantial differences in identified risk factors compared to the general population, with age-adjusted mortality being approximately 50% lower within UK Biobank.[38]

There is an increasing amount of routine data, particularly as GP data availability increases across the UK, that is now available to the research community. There are many important developments and initiatives that can support research into MLTC at scale.[39] Detailed-long term data on participants is required to study disease trajectories and the impact of disease clusters on patient and population outcomes.

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[33] Chudasama YV, *et al.* (2020). *Impact of COVID-19 on routine care for chronic diseases: A global survey of views from healthcare professionals* Diab Met Syndrom **14(5)**, 965–967.

[34] https://isaric.tghn.org/

[35] https://www.hdruk.ac.uk/news/a-new-population-wide-health-data-resource-to-accelerate-research-on-covid-19-and-cardiovascular-disease-in-england/

[36] https://www.opensafely.org/

[37] https://www.phosp.org/

[38] Fry A, *et al.* (2017). *Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population*. Am J Epidemiol **186(9)**, 1026-1034.

[39] Developments include: NHS Digital General Practice Extraction Service, OpenSAFELY, QResearch, Clinical Practice Research Datalink, English Primary Care Research Network, Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) and Secure Anonymised Information Linkage (SAIL) Databank.

HDR UK has funded a national multimorbidity implementation project, which aims to harmonise data across five geographies, covering 20 million people.[40] Within this the Wales Multimorbidity Cohort (WMC) follows up the entire population of Wales for 20 years using multiple data streams, including linked census data.[41] One of the principal aims of WMC is to identify disease clusters that are important in terms of premature mortality or excess health service usage, with a particular focus on health inequalities. The WMC design concept proved its utility when it was rapidly adapted to provide near real-time analysis of the spread, impact and evaluation of countermeasures of the COVID-19 pandemic to the Welsh Government COVID-19 Technical Advisory Group and onwards to SAGE, following additional investment from UKRI MRC.[42]

Professor Lyons emphasised that the WMC was brought about through embracing the recommendations of the Academy's 2016 Team Science report and creating a UK-wide team science culture.[43] More than 100 researchers from universities across the UK have remote analysis access to WMC and its COVID-19 derivative. He also highlighted the members of the public who have been embedded within the research team from the beginning and have helped ensure that the focus is on issues important to patients.

Understanding the biological pathways underlying MLTC

Understanding the biological pathways underlying MLTC presents an opportunity to generate new drug targets, that can be harnessed by the pharmaceutical industry and wider life sciences sector to create transformative new medicines. Professor Janet Lord FMedSci, Professor of Immune Cell Biology at the University of Birmingham, discussed how further understanding of biological mechanisms is opening up new opportunities for interventions that could target pathways to treat multiple conditions in her field of ageing research.

Professor Lord described that, in an analysis of all unplanned admissions to a UK hospital over a six-month period, there was a median of six co-occurring conditions per patient, and the length of stay in hospital had a strong positive association with MLTC. Professor Lord suggested that MLTC could be used as an indicator of how well or poorly someone has aged.

Conditions often do not arise individually, but instead in common clusters (e.g. neuropsychiatric, musculoskeletal and cardiometabolic clusters). Clustering indicates that there may be processes common to these diseases that influence how they arise and impact the individual. Age-related diseases, such as cancer and heart disease, are researched and treated individually, but if ageing is one of the key risk factors, tackling

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[40] https://www.hdruk.ac.uk/projects/national-multimorbidity-resource/

[41] Lyons J, *et al.* (2021). *Protocol for the development of the Wales Multi-morbidity e-Cohort (WMC): data sources and methods to construct a population-based research platform to investigate multi-morbidity.* BMJ Open **11**, e047101.

[42] Lyons J, et al. (2020). Understanding and responding to COVID-19 in Wales: protocol for a privacy protecting data platform for enhanced epidemiology and evaluation of interventions. BMJ Open **10**, e043010.

[43] Academy of Medical Sciences (2016). *Improving recognition of team science contributions in biomedical research careers.* https://acmedsci.ac.uk/file-download/6924621

the ageing process may provide targets for treating multiple conditions.

For example, senescent (or exhausted) cells build up as individuals age in various tissues and are causally implicated in generating age-related phenotypes. Studies in mice found that removing senescent cells prevented age-related conditions, such as sarcopenia, osteoporosis and cataracts, and had broad benefits in physiological ageing.[44,45] This has led to the development of 'senolytics', which kill senescent cells. A first-in-human trial for patients with idiopathic pulmonary fibrosis, a severe disease of the lungs, found that a short period of senolytic therapy improved patients' frailty and mobility.[46] Considering the potential broad physiological benefits, targeting ageing may present targets or pathways that can be used to treat or prevent MLTC.

Targeting ageing processes may also be relevant to COVID-19. Professor Lord highlighted that studies of UK Biobank subjects found that an increased biological age, rather than chronological age, is a better predictor of COVID-19 severity.[47]

Including more patients with MLTC in clinical trials

Including patients with complex medical conditions in clinical trials can be challenging, but provides significant opportunities. Professor Deborah Ashby OBE FMedSci, Director of the School of Public Health at Imperial College London, discussed the practical implications of involving these patients in clinical trials, and how the inclusion of patients with MLTC in clinical trials might be made standard practice.

There are a number of challenges to undertaking trials involving patients with MLTC, including:
- Greater variability due to patient heterogeneity, necessitating larger sample sizes.
- More complex entry criteria, which may mean the usual patient recruitment pathways are not sufficient.
- The lack of connection between treatment pathways for co-existing conditions, which sometimes leads to uncoordinated, single-condition thinking and approaches.
- Increased challenges in scheduling follow-up visits due to the more varied needs of participants.
- Consideration of pharmacological interactions of medicines already used by trial participants with MLTC and the potential impact on their daily regime.
- Increased difficulty in studying some endpoints, for example, in patients with sight or hearing loss, or dementia where it may be hard to use the common assessment tools.

However, Professor Ashby highlighted the many advantages to doing trials in MLTC. For example, trials incorporating MLTC would better meet the needs of patients. In addition, patients and their carers are experts in their own conditions, providing a valuable source

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[44] Baker DJ, *et al.* (2011). *Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders.* Nature **479**, 232–236.
[45] Baker DJ, *et al.* (2016). *Naturally occurring p16Ink4a-positive cells shorten healthy lifespan.* Nature **530**, 184–189.
[46] Justice JN, *et al.* (2019). *Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study.* EBioMedicine **40**, 554-563.
[47] Kuo C, *et al.* (2020) *COVID-19 severity is predicted by earlier evidence of accelerated aging.* medRxiv. Preprint. 2020 Jul 11.

of information. Such trials would also provide better data for prescribers to inform treatment recommendations.

When considering more complex trials, it is essential to articulate the research questions clearly to inform trial designs. For example, trials could consider whether a well-established therapy for a particular condition can be used in patients who also have another condition, or determine the best treatment strategy for patients with a common cluster of co-occurring conditions. Professor Ashby emphasised the importance of understanding the pharmacology and interactions of medicines used by people with MLTC to understand potential ADRs. This will enable the choice of medicines, dosages, routes of administration to be modified appropriately, and promote the consideration of alternative interventions, such as analogues for non-pharmacological interventions and changes to make daily regimes more manageable.

It is important to consider patient populations and trial design. A trial focusing on a single condition should at least systematically consider common co-morbidities. However, trials with very simple entry criteria may require increased participant numbers to meet sufficient power for particular disease combinations, which will require careful and well thought out recruitment strategies. It was suggested to first consider common clusters and those with common aetiologies. Professor Ashby suggested a need for both 'explanatory trials' to fully understand the impact of an intervention with a homogenous patient population and 'pragmatic trials' to determine the preferred treatment strategies in real-world populations.

Annex II – Attendee list

Chairs
Professor Paul Elliott CBE FMedSci, Professor of Epidemiology and Public Health Medicine, Imperial College London
Professor Pernille B. Laerkegaard Hansen, Senior Director, Head of Bioscience Renal, AstraZeneca and Professor of Cardiovascular and Renal Research, University of Southern Denmark

Speakers
Professor Deborah Ashby OBE FMedSci, Chair in Medical Statistics and Clinical Trials, Imperial College London
Dr Jennifer Bostock, Patient representative
Dr Cheryl Gowar, Patient representative
Professor Kamlesh Khunti FMedSci, Head of Department and Professor of Primary Care Diabetes and Vascular Medicine, University of Leicester
Professor Janet Lord FMedSci, Director of the MRC-Versus Arthritis Centre for Musculoskeletal Aging Research and Professor of Immune Cell Biology, University of Birmingham
Professor Ronan Lyons, Clinical Professor of Public Health, Swansea University
Dr Sheuli Porkess, Executive Director, Research, Medical and Innovation, The Association of the British Pharmaceutical Industry
Professor Alan Silman FMedSci, Professor of Musculoskeletal Health, University of Oxford

Spark Talk Speakers
Professor John Gallacher, Professor of Cognitive Health, University of Oxford and Director, Dementias Platform UK
Professor Valerie O'Donnell FLSW FMedSci, Director, Division of Infection and Immunity and Co-Director, Systems Immunity Research Institute, Cardiff University
Professor Robert Unwin, Senior Medical Director in Early Clinical Development, AstraZeneca
Professor Miles Witham, Professor of Trials for Older People, Newcastle University

Attendees
Dr André Amaral, Lecturer in Respiratory Epidemiology, Imperial College London
Dr Sue Bailey, Strategic Partnership and Early Asset Director, Bristol-Myers Squibb
Professor Deborah Baines, Professor of Molecular Physiology, St George's, University of London
Dr Rebecca Bendayan, MRC/NIHR Research Fellow, Kings College London
Dr Suchira Bose, Neurodegeneration Target and Discovery Leader, Eli Lilly
Professor Chas Bountra OBE, Pro-Vice Chancellor for Innovation and Professor of Translational Medicine, University of Oxford
Professor Carol Brayne CBE FMedSci, Professor of Public Health Medicine, University of Cambridge
Helen Brock, Programme Manager – Adults & Older Adults, Public Health England
Dr Emma Chambers, Lecturer, Queen Mary University of London
Dr Briana Coles, Research Fellow in Biostatistics/Epidemiology, University of Leicester
Professor Richard Coward, Professor of Renal Medicine, University of Bristol
Professor Christian Delles, Professor of Cardiovascular Prevention, University of Glasgow
Dr Anna Durans, Research Programme Manager, Versus Arthritis
Professor Majid Ezzati FMedSci, Professor of Global Environmental Health, Imperial College London
Professor Andrew Farmer, Professor of General Practice, University of Oxford
Professor Sir Michael Ferguson CBE FRS FRSE FMedSci, Regius Professor of Life Sciences, University of Dundee

Professor Gary Ford CBE FMedSci, Chief Executive Officer, Oxford Academic Health Science Network

Belen Granell Villen, Quality and Safety Policy Executive, The Association of the British Pharmaceutical Industry

Dr Stephen Gray, Portfolio Manager, Wellcome Trust

Professor Bruce Guthrie, Professor of General Practice, University of Edinburgh

Professor Paul Harrison, Professor of Psychiatry, University of Oxford

Dr Branwen Hennig, Senior Portfolio Lead Population Health, Wellcome Trust

Mr Steve Hoare, Quality, Regulatory Science & Safety Policy Director, The Association of the British Pharmaceutical Industry

Dr Neha Issar-Brown, Director, Research, Policy and Innovation, Fight For Sight

Dr Farideh Jalali, MRC Skills Development Fellow, University of Manchester

Ms Susan Kay, Chief Executive, Dunhill Medical Trust

Dr Katherine Keenan, Senior Lecturer in Demography/Population Geography, University of St Andrews

Dr Steven Kiddle, Principal Health Informatics Data Scientist, AstraZeneca

Emily Lam, Patient representative

Professor Nick Lemoine FMedSci, Medical Director, NIHR Clinical Research Network

Dr Ian Lewis, Head of Strategy and Initiatives, National Cancer Research Institutes

Karen Ma, Patient representative

Dr Ian Maidment, Reader in Clinical Pharmacy, Aston University

Dr Charlotte Paddison, Senior Fellow, Nuffield Trust

Francesco Palma, Patient representative

Dr Jonathan Pearson-Stuttard, Wellcome Trust Clinical Research Fellow, Imperial College London and Head of Health Analytics, Lane Clark & Peacock

Professor Niels Peek, Professor of Health Informatics, University of Manchester

Professor Rafael Perera, Professor of Medical Statistics, University of Oxford

Tom Porter, Strategy Director, Lane Clark & Peacock

Gabriel Rogers, Technical Adviser (Health Economics), National Institute for Health and Care Excellence

Dr Naj Rotheram, Global Medical Expert Specialist, Boehringer Ingelheim

Professor Sir Nilesh Samani FMedSci, Medical Director, British Heart Foundation

Professor Sandosh Padmanabhan, Professor of Cardiovascular Genomics and Therapeutics, University of Glasgow

Dr Carolyn Sharpe, Public Health Registrar, Public Health England

Steven Smith, Grants Manager, Fight For Sight

Professor Reecha Sofat, Professor of Clinical Pharmacology, University College London

Dr Charlie Tomson, Trustee, Kidney Research UK

Professor Rhian Touyz FMedSci, Director, Institute of Cardiovascular & Medical Sciences, British Heart Foundation Chair of Cardiovascular Medicine, University of Glasgow

Professor José Valderas, Professor of Health Services and Policy Research, University of Exeter

Dr Beverley Vaughan, Programme Director, University of Oxford

Professor Brian Walker FRSE FMedSci, Pro-Vice-Chancellor, Research Strategy and Resources, Newcastle University

Dr Lauren Walker, NIHR Academic Clinical Lecturer in Clinical Pharmacology and Therapeutics, University of Liverpool

Joshua Wheeler, Policy and Business Analyst, OptumLabs

Professor Chris Whitty CB FMedSci, Chief Medical Officer for England

Dr Graeme Wilkinson, Head of Virtual Drug Discovery, Medicines Discovery Catapult

Dr Louise Wood CBE, Director of Science, Research and Evidence, Department of Health and Social Care

Dr Kirsty Wydenbach, Deputy Unit Manager / Expert Medical Assessor, Clinical Trials Unit, Medicines and Healthcare products Regulatory Agency

Dr Naho Yamazaki, Head of Policy and Engagement, Health Research Authority

Dr Anna Zecharia, Director of Policy & Research, British Pharmacological Society

Secretariat
Dr Emma Laycock, Policy Officer, Academy of Medical Sciences
Dr James Squires, FORUM Policy Manager, Academy of Medical Sciences
Dr Claire Cope, Head of Policy, Academy of Medical Sciences
Rachael Cartwright, Project Manager, Medical Research Council
Dr Ivan Pavlov, Board Secretary and Lead on Multimorbidity, Population and Systems Medicine
Board, Medical Research Council
Dr Jane Strom, Science Manager, Medical Research Council
Leanne Dew, Principal Research Analyst, Department of Health and Social Care
Dr Madina Kara, Senior Research Collaboration Manager, National Institute for Health Research
Dr Natalie Owen, Senior Research Programme Manager, National Institute for Health Research

Annex III – Agenda

Monday 19 October 10.00 – 13.00 - **Day 1**	
10.00-10.10	**Welcome and introduction from co-chairs** Professor Paul Elliott CBE FMedSci, Professor of Epidemiology and Public Health Medicine, Imperial College London Professor Pernille B. Laerkegaard Hansen, Senior Director, Head of Bioscience Renal, AstraZeneca and Professor of Cardiovascular and Renal Research, University of Southern Denmark
	Session 1: The multimorbidity research landscape
10.10-10.20	**A patient perspective of multiple long-term conditions** Cheryl Gowar & Jennifer Bostock, Patient representative
10.20-10.30	**Multimorbidity as a cross-sector opportunity – progress since the Academy's 2018 report** Professor Alan Silman FMedSci, Professor of Musculoskeletal Health, University of Oxford, Member of the 2018 report working group and Chair of the Academy's 2019 workshop '*Improving the prevention and management of multimorbidity in sub-Saharan Africa'*
10.30-10.40	**Moving beyond one target for one disease – what does industry need to incorporate multimorbidity approaches?** Dr Sheuli Porkess, Executive Director, Research, Medical and Innovation, The Association of the British Pharmaceutical Industry
10.40-10.50	**Data-driven approaches at the heart of understanding multiple long term conditions – harnessing existing assets and creating new ones** Professor Ronan Lyons, Clinical Professor of Public Health, Swansea University
10.50-11.00	**How understanding biological pathways is providing new opportunities to develop interventions** Professor Janet Lord FMedSci, Director of the Institute of Inflammation and Ageing, University of Birmingham
11.00-11.10	**How do we facilitate multimorbidity-inclusive clinical trials?** Professor Deborah Ashby OBE FMedSci, Chair in Medical Statistics and Clinical Trials, Imperial College London
11.10-11.20	**Break**
	Session 2: Seizing the opportunities of multimorbidity-inclusive translational research

11.20-12.00	**Parallel breakout sessions (1)**
	
	- Option A: Data-driven approaches to disease clustering:
	    o How do we make the most of existing academic or industry data sources and infrastructure?
	    o What new data sources, infrastructure or analytic tools might we require?
	    o What other elements of the research ecosystem need to be changed to streamline disease clustering research and link it to commercial R&D?
	- Option B: Biological mechanisms of comorbidities
	    o How do we go about identifying new pathways that link multiple conditions?
	    o What key evidence sources are needed to enable these pathways to be used to identify novel drug targets?
	    o How do we incentivise these targets being pursued for drug discovery programmes?
	- Option C: Incorporating patients with complex medical histories into clinical trials
	    o What are the key considerations that make it challenging to incorporate these patients in to trials?

	o What tools would we need to overcome these challenges? o Assuming these challenges can be overcome, where do the major opportunities lie for trials involving patients with multiple long term conditions?
12.00-12.10	**Break**

12.10-12.50	**Parallel breakout sessions (2)**
	
	- Option A: Data-driven approaches to disease clustering:
	   o What elements of the research ecosystem need to be changed to streamline disease clustering research and link it to commercial R&D?
	   o What new data sources, infrastructure or analytic tools might we require?
	   o How do we make the most of existing academic or industry data sources and infrastructure?
	- Option B: Biological mechanisms of comorbidities
	   o How do we incentivise unifying pathway targets being pursued for drug discovery programmes?
	   o What key evidence sources are needed to enable these pathways to be used to identify novel drug targets?
	   o How do we go about identifying new pathways that link multiple conditions?
	- Option C: Incorporating patients with complex medical histories into clinical trials
	   o Where do the major opportunities lie for trials involving patients with multiple long term conditions?
	   o What are the key considerations that make it challenging to incorporate these patients in to trials?
	   o What tools would we need to overcome these challenges?

12.50-13.00	**Summary and chairs' remarks**

Thursday 22 October 11.00 – 13.00 - Day 2	
11.00-11.10	**Welcome and introduction from co-chairs** Professor Paul Elliott CBE FMedSci, Professor of Epidemiology and Public Health Medicine, Imperial College London Professor Pernille B. Laerkegaard Hansen, Senior Director, Head of Bioscience Renal, AstraZeneca and Professor of Cardiovascular and Renal Research, University of Southern Denmark
	Session 3: Embedding multimorbidity into research pathways
11.10-11.30	**Reporting back from breakout groups** *The facilitator/rapporteur of each breakout group will be asked to report back the key points from their breakout group (2-3 minutes each).*
11.30-11.50	**Rising to the challenge of multimorbidity and considering the impact of COVID-19** Professor Kamlesh Khunti FMedSci, Professor of Primary Care Diabetes and Vascular Medicine, University of Leicester
11.50-12.50	**Plenary discussion: How do we integrate these different research strands across the life sciences sector to embed multimorbidity into research pathways?** *Key questions* - *How can the UK life science sector support multimorbidity research at all levels of the translational pathway?* - *What are the practical next steps to move forward the multimorbidity agenda?*
12.50-13.00	**Summary and chairs' remarks**