

Tackling multimorbidity at scale: Understanding disease clusters, determinants & biological pathways

Call specification

Summary

Multimorbidity is associated with a reduction in quality of life, increased use of health services and reduced life expectancy. As the number of conditions an individual has increases, so does the likelihood of increased healthcare costs¹. Multimorbidity has suffered scientifically from being seen as a random assortment of diseases, making it difficult to address. However, with new understanding of the impact of various factors (including biological, social, behavioural, environmental and others), multimorbidity can be seen as series of non-random clusters of disease. While some clusters are obvious (e.g. obesity with cardiovascular disease-osteoarthritis & several cancers), others need further identification (particularly physical and mental health comorbidities) and follow on mechanistic exploration. This will require new multi-disciplinary approaches to mapping and tackling multimorbidity, at scale.

Better understanding of disease clusters and underlying mechanisms, taking a broad approach that can encompass the biological, and wider determinants as appropriate, will make clinical, public health and scientific progress more achievable.

Research to explore disease clusters and associations, and to better measure and understand multimorbidity across the [UK population has already begun](#) via the Medical Research Council (MRC) - National Institute for Health Research (NIHR) [pump-priming initiative](#) and by Health Data Research UK (HDR UK), through its [national multimorbidity resource](#) project.

However, large multi-disciplinary research collaborative efforts are needed to address current research gaps and achieve the required cohesion in this field. To this end, this [Strategic Priorities Fund](#) (SPF) research call, jointly funded by the UK Research and Innovation (UKRI) and the Department of Health and Social Care (DHSC) through the National Institute for Health Research (NIHR), will bring together multi-disciplinary collaborations with a range of scientific, methodological, and clinical knowledge and skills to build manageable, focused “**Multimorbidity Research Collaboratives**”. These collaboratives will be expected to have strong patient involvement, as benefits the remit of the project, and add significant understanding to a broad range of topics including, for example:

- Identification of new disease clusters
- Multimorbidity over different stages across the life-course taking a comprehensive multi-disciplinary approach
- Discovery, validation and targeting of underlying mechanistic and

¹ [Multimorbidity: a priority for global health research \(Academy of Medical Sciences report, 2018\)](#).

pathobiological pathways.

Recognising the potential to identify new patterns of multimorbidity and contributing factors, and the more advanced nature of research on more established multimorbidity clusters, the call is designed in two streams:

- For those groups that need time to consolidate existing data or collaborations and/or obtain preliminary data there is an option to apply for a rapid and modest “**Consolidator grant**”. These grants will serve as a test bed, bringing new disciplines together and provide proof-of-concept data, enabling the best groupings and ideas to mature to a second “**Research Collaborative award**” stage.
- For those other groups that have already developed multi-disciplinary networks and supporting data, there will be the option to move straight to the “**Research Collaborative award**” stage.

1. Background

Research on multimorbidity has been identified as an urgent priority for the UK and globally following the [Academy of Medical Sciences’ \(AMS\) report on Multimorbidity](#) and the follow up [workshop](#) jointly organised by the MRC, the NIHR, AMS and Wellcome. Multimorbidity is defined by this report as the co-existence of two or more chronic conditions in a single individual, including mental and physical conditions and long duration infectious diseases.

Multimorbidity is increasing, both in absolute terms and relative to single morbidity. A large study in Scotland reported that nearly 65% of those aged 65-84 years were identified as having multiple long-term conditions, and this increased to 82% of those over 85 years.

Multimorbidity is a life-course issue, also affecting children, young people and younger working age groups, with almost 1 in 5 people aged 25-64 having more than one long-term condition². Complex multimorbidity (4+ conditions) is expected to almost double in the next 15 years, with recent modelling showing an estimated rise from 9.8% of adults over 35 years in 2015 to 17% in 2035³. The impact of social, environmental and behavioural factors over the life course will be crucial to understanding disease clusters and trajectories, alongside biological pathways involved in the development of multimorbidity.

While changing demography accounts for some of the rise in multimorbidity, there are factors which can compound the challenge. For example, we know that people living in areas of deprivation are more likely to be living with multiple long-term conditions compared with their counterparts in less deprived areas⁴; and that obesity, levels of which have risen over the last two decades⁵, plays a role in several long-term conditions such as hypertension, type 2 diabetes and musculoskeletal disorders.

Research to overcome the challenge of multimorbidity has suffered from a failure to recognise predictable clusters of disease, instead viewing patients with multiple long-term conditions as having a random assortment of conditions. In reality, multimorbidity is a

² Barnett et al. (2012) Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet* 380(9836), 37-43.

³ Kingston et al. (2018) Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. *Age and Ageing*, 47, 374–380.

⁴ Cassel et al. (2018) The epidemiology of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*, 68(669):e245-e251.

⁵ <https://files.digital.nhs.uk/publication/0/0/obes-phys-acti-diet-eng-2018-rep.pdf>

series of non-random clusters of disease. Some clusters are known, for example diabetes, stroke, heart disease and foot ulceration and these can lend themselves to mechanistic exploration of common biological pathways. Others are yet to be identified and may be influenced by a range of factors including behavioural, psychological, social determinants and underpinning biological pathways which need further understanding through exploration of large interlinked datasets.

The UK is in an excellent position to lead multimorbidity research with multiple cohorts (the UK Biobank, Million Women, SAIL), social and behavioural longitudinal studies (such as the English Longitudinal Survey of Ageing, Understanding Society dataset), large-scale NHS datasets, excellence in artificial intelligence (AI) and a diverse population. There is an urgent need to accelerate action across the UK research landscape on multimorbidity research.

The initiative:

- is supported through the SPF, led by the UKRI's MRC, and is jointly funded by the Department of Health and Social Care (DHSC) through the NIHR;
- builds on and continues extensive collaboration between the MRC, the Economic and Social Research Council (ESRC) the Engineering and Physical Sciences Research Council (EPSRC) and the NIHR;
- has an ambition, working with HDR UK, to have an open approach to the reuse of data created and managed by awardees.

2. Objectives

The overall objective is to bring together world-leading multi-disciplinary expertise in epidemiological research, mechanistic, and data science to catalyse multimorbidity research nationally and at scale through supporting a portfolio of **Research Collaboratives**.

It is envisaged that successful collaboratives will consolidate expertise, including from single disease domains, towards building more integrated, multi-disease resources for future exploitation, which may be identification of new clusters, biological, social and environmental determinants and mechanisms and/or detailed examination of multimorbidity disease pathobiologies and trajectories. We expect the studies supported to:

- **Move away from a one-disease, one mechanism approach** by identifying and mapping clusters of disease, understanding the trajectories within clusters and understanding the cluster determinants, mechanisms and underpinning pathobiological pathways.
- **Take a holistic approach** by examining the wider determinants of clusters of multiple long-term conditions, including the dynamic within and between biological, environmental, psychological and socioeconomic determinants in the development, trajectories and prevention and management of multiple long-term conditions.
- **Utilise and build on experience and expertise** such as in acquiring repeat, real-time biological measures from well-powered population and clinical cohorts, extensive patient phenotyping and stratification to capture and interrogate truly dynamic disease-disease interactions, including transient

changes in health.

We expect the collaboratives to add significant understanding to a broad range of topics (see Remit and Scope for details) using multimodal data sources to deliver research that lays the foundations for developing interventions. The call offers the opportunity to enhance traditional epidemiological methods and promote new approaches to exploring multimorbidity. This could be achieved through data collection, harmonisation and analysis from multiple sources (such as omics, clinical and stratified medicine platforms, primary care, prescription, administrative, social and environmental datasets).

The collaborations funded through this initiative are expected to collectively develop and adopt a methodological framework and principles for data-driven discovery and create a shared data resource to enable future research into multimorbidity, facilitated by the [Health Data Research Innovation Gateway](#).

The ultimate aim following on from this work is to begin to tackle large scale problems and advance research on multimorbidity across many areas including: finding solutions for the UK health and social care sector; improving the quality of life and health outcomes for people with multiple long-term conditions; exploring steps for new approaches and future industry collaborations to diagnose disease early, progress drug development and address the burden of polypharmacy; and to reduce progression to a greater number of conditions.

3. Remit and scope

The scope of the call includes, but is not limited to, the following broad research topics:

- **Identify and describe new disease clusters** by examining the co-existence and co-development of pathological processes in the general population and well-defined population and patient sub-groups
- **Multimorbidity at different stages of the life course**, including early life determinants of defined multimorbidity clusters as well as biological, environmental, behavioural and social determinants of disease aetiology and progression
- **Uncovering, validating and targeting shared determinants and mechanistic pathways** of multiple diseases or disease clusters for multimorbidity treatment, management and prevention
- Studies addressing **early detection/prediction** of multimorbidity and longitudinal aspects of disease progression, including timing and direction of causal relationships, interactions and variations in the “known” pathobiological pathways involved in disease progression; and identifying new promising therapeutic options to tackle multimorbidity.

While some proposals may be ideally placed to address one or more of the above potential evidence gaps, it is not expected that all topics will be covered in one proposal. However, all proposals are expected to consider the following:

- Projects that focus on complex multimorbidity with several long-term conditions, rather than just two co-morbidities would be particularly welcome.
- Projects aimed at understanding the underlying mechanisms and pathways should

extend beyond purely observational work or association studies and should ideally aim to inform and / or contribute towards identification of future translation pathways. Where relevant, identified mechanisms may go beyond only biological signalling and reflect complex interactions between an individual and their environment.

- Applicants are encouraged to consider their research in the context of the UK health care systems to identify pathways to transformation to better deal with the burden of multimorbidity.
- Applicants should demonstrate a strong intention to work with other successful groups funded by this call to create synergies between research projects, share learning and expertise across consortia, build capacity and maximise impact of the funding overall.
- Applicants are also encouraged to carefully consider patients' and affected populations' perspective on living with multimorbidity. Applicants will be required to include in their proposals clearly articulated Patient and Public Involvement (PPI) plans for continuous interactions with patient groups throughout the project. Useful information on how to develop PPI plans, engage with patient groups and descriptions of best practices could be found at the INVOLVE website [here](#).
- Applicants should consider how their research might address the need to reduce health inequalities or justify why they have not done so.
- All proposals are expected to be led by a UK-based principal investigator, but international links and collaborations are also welcome (see section 7 for further details on eligibility).

4. Funding and expectations

This is a two-stream competition to support:

- work to build collaborations, obtain preliminary data and/or validate approaches via modest sized **Consolidator grants** before progressing to a full *Research Collaborative award* stage,

or

- directly **Research Collaborative** proposals, where maturity of research plans, resources and capacity can be demonstrated without the need of the further development stage through the Consolidator grant (see flow diagram below).

At the outline stage, applicants have the choice to apply for a *Consolidator grant* or go directly for a full *Research Collaborative award*, pending initial panel review. Successful recipients of a *Consolidator grant* would be expected to apply for a full *Research Collaborative award* at the end of the six-month period. The two-stage process aims to ensure that all Collaboratives supported through this initiative convincingly demonstrate the feasibility of their approach and confidence in the study concept at the outset and/or are supported to achieve it via the Consolidator grant stage. The Consolidator grants will also serve as a test bed to bring new disciplines, such as AI, to provide proof-of-concept.

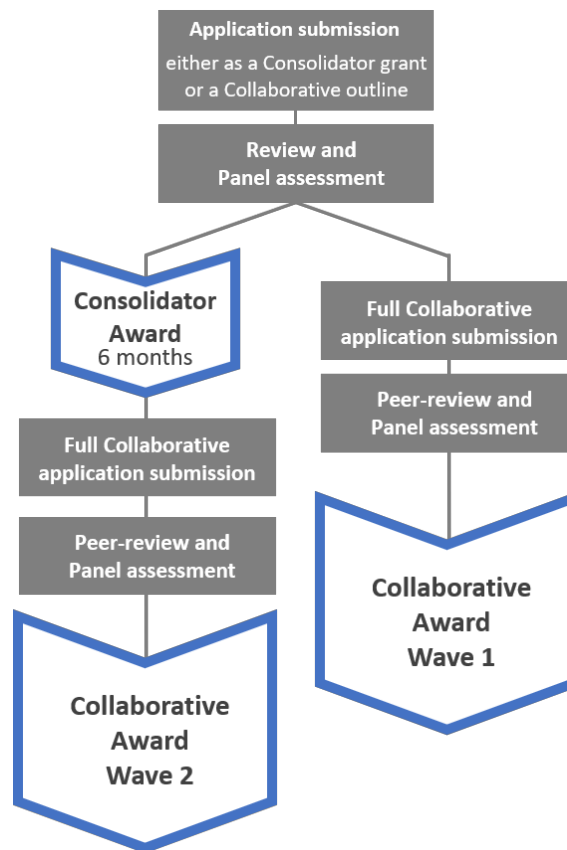


Figure 1. Call schematic showing two streams of competition for Research Collaborative awards

4.1 Consolidator grants

Up to £1.5 million is available for Consolidator grants. These will be funded for the fixed duration of 6 months; the award amount will be up to £100,000⁶ (RC contribution).

All awards are expected to be collaborative and multi-disciplinary in nature. Research teams may build on existing relationships or develop a new collaboration between different researchers and/or resources, for instance, grouping of investigators with single disease expertise branching out to extend their work through newly established links with scientists working on different diseases, methodologists, statisticians, researchers from other disciplines, carers and patient groups.

The grants can therefore be used to:

- consolidate partnerships and bring in experts who might not traditionally view themselves as multimorbidity researchers
- perform rapid linkage and analyses of existing data including, for example, health data, population and environmental datasets
- obtain preliminary data or proof-of-principle evidence
- identify key gaps that would be addressed at the full Research Collaborative stage
- verify their approaches towards addressing those gaps.

⁶ The funders' contribution (described as 'RC contribution' here and within Je-S) for Consolidator grants should not exceed £100,000

Please note that although necessary networking events may be supported as part of these grants, funding is primarily intended to support relevant research expenses and not to be spent solely on engagement activities (e.g. workshops, conference attendance, meetings etc.).

Applicants should clearly demonstrate the balance and proportionality in partners' roles and responsibilities and the potential of the group to scale up their research and develop a competitive Collaborative award application by the end of this six-month grant.

It is expected that while some successful recipients of a Consolidator grant may proceed to the Research Collaborative award stage, some may require a longer period for maturation and may be more suitable for response mode funding.

4.2 Research Collaborative awards

Research groups with more mature collaboration links; ownership or existing access to the relevant datasets; and sufficient evidence, underpinned by strong preliminary data, of their ability to perform multimorbidity research at scale, can apply for the Wave 1 Research Collaborative awards, bypassing Consolidator stage. These awards will provide substantial investment to support ambitious studies performed by combinations of partners. Research Collaboratives may include, where appropriate, industry partners, in which case they would require to submit their application as a [MRC Industry Collaboration Agreement](#) (please read about the MRC Policy on academic-industry collaborations [here](#)). This competition seeks to support a balanced research portfolio of several Research Collaboratives for 2-4 years (£3-5m each).

All awards will be funded on the basis of 80% of the full economic cost (see [Section 3. Resources in the MRC Guidance for Applicants](#)). Collaborative awards are not capped but applicants should note that we would like to fund multiple collaboratives within the funding envelope. The funders expect applications to demonstrate the maximum research impact from the investment, and applicants are advised that value for money is an important assessment criterion.

NHS* costs

Applicants should refer to the [AcoRD guidance](#) to ensure that research costs, NHS treatment costs and NHS support costs are correctly attributed. Applications involving NHS costs are required to include a completed [SoECAT form which can be downloaded from the NIHR website](#).

** This guidance is applicable to England, Wales, Scotland and Northern Ireland.*

5. Application process

The MRC will administer this call on behalf of the funders. Applicants are advised to ensure their host research organisation is allowed sufficient time to complete the final submission of the proposal through Je-S, by 16:00 (GMT), on the advertised call closing date 11th February 2020. For the purpose of this call when applying on Je-S, please select:

- **council:** *MRC*
- **document type:** *standard proposal*
- **scheme:** *research grant*

call: *Tackling multimorbidity at scale: Understanding disease clusters, determinants & biological pathways*

Please note:

- the 'Case for Support' should be submitted on the call-specific template, which can be downloaded [here](#). Applicants are advised to fill in the template and upload it to the attachment section of the Je-S proposal form, selecting the mandatory attachment type 'Case for Support'.
- The '[Case for Support template](#)' serves as the application form for both *Consolidator grants*, and as an outline for the *Research Collaborative awards*.

When submitting their proposals, applicants will be requested to indicate (within the Case for Support template), if they wish to apply for the *Consolidator grant* or want their application to be treated as an outline of the *Research Collaborative awards*. The applicants' choice will be taken into consideration when processing the applications, but the Panel reserves the right to triage and allocate applications to the appropriate category following assessment (see Section 6).

Applicants submitting an outline of the Research Collaborative proposal are advised that they are expected to estimate the costs of the *Research Collaborative award* within the '[Case for Support template](#)' and at this stage are **not** required to detail any costs within the Je-S proposal form. The outline application should be submitted as '**Zero**' cost through Je-S to MRC. Any proposed Researcher Co-Investigator (RCo-I) staff in the Research Collaborative outline should be added a Co-Investigator (Co-I) in the Je-S form at this stage. Applicants are advised to make a note of that in their Proposal Cover Letter letting the Panel know if any Co-I will be a RCo-I in the full proposal.

Please note, because the same Je-S form is being used for both Consolidator applications and Research Collaborative outlines, applicants submitting outline proposals should detail the duration of their suggested Research Collaboratives in the '[Case for Support template](#)', and in the *Project Details* section of the Je-S form put the project duration as 6 months.

Applicants submitting a *Consolidator grant* application are requested to provide a breakdown of the proposed expenses for their 6 month consolidator stage period when completing the Je-S form, and also to indicate an expected cost of their future *Research Collaborative award* in the relevant section of the '[Case for Support template](#)'.

Applicants will be notified of the decision, following the panel meeting scheduled for March/April 2020.

Successful Research Collaborative outlines will be invited to submit full proposals to a deadline in May 2020 (to be confirmed and communicated to the applicants later) to be considered by the Funding Panel which is expected to meet during summer 2020 (Wave 1).

Successful Consolidator grant applicants will be invited to submit their full Research Collaborative applications by the end of their Consolidator grant to be assessed by the Funding Panel for the wave 2 Research Collaborative awards in January 2021 (TBC).

Applicants are advised that successful Consolidator grants will be expected to start no later than 1st May 2020. There will be no flexibility to delay the start date of the grants and the awards may lapse if not started in time. Consolidator grants are fixed in duration and cannot be extended.

5.1 Alignment with the existing health data infrastructure

It is expected that all data generated or curated within these awards are made accessible to the broad scientific community. Applicants must carefully consider how they will manage the safe, responsible and ethical access to the data generated within their proposals. To ensure the wider impact of these SPF awards, and further utility of the multimorbidity datasets generated and/or used, successful Research Collaboratives will be expected to support the creation of a nation-wide integrated health data resource. Existing multimorbidity data used in the proposed research, as well as any new data generated using these funds, should be made available through the currently developed [Health Data Research Innovation Gateway](#). We, therefore expect each funded team, as a data custodian, to subscribe to the UK Health Data Research [Alliance's Terms & Conditions](#) on information governance, ethics, intellectual property rights and commercial models. Subscription to the Alliance Principles of Participation (as detailed [here](#)) and membership of the Alliance is strongly encouraged for all recipients of the Research Collaborative awards. Otherwise applicants should provide clear justification of the alternative mechanism by which they intend to make their data discoverable and accessible by others. Applicants can register their interest in becoming a member of the Alliance [here](#).

Please note, applicants are advised to include dedicated, named Data Manager / Officer expertise in their structure. This will ensure that the technical knowledge, expertise and support at the senior manager level are available for the grouping overseeing internal interactions on data-related issues between the participants and an interface between the collaborative, data gateway and the potential external users.

6. Assessment process

All applications for the *Consolidator grants* and outlines of the *Research Collaborative awards* will be reviewed by an external Expert Funding Panel which will convene in March/April 2020 to make funding recommendations on the Consolidator grants and agree which teams applying for the Research Collaborative grants are invited to submit full proposals.

Full applications for the Research Collaborative award will be peer-reviewed and assessed at the next Panel meeting (expected to be held during summer 2020 for wave 1 and in January 2021 for wave 2). A separate full application, assessment criteria and guidance will be produced for the full stage Research Collaborative awards ahead of the respective full stage Panel meetings.

For this call, applicants should carefully consider the criteria below, which will be taken into account by the Expert Funding Panel when assessing the proposals and their suitability for either a *Consolidator grant* or to progress directly to the full *Research Collaborative award* stage. While the applicants' choices will be considered, the routing of applications via either stage will be based on the Panel's assessment of the strength of the case for support and the evidence provided to address the relevant criteria below:

Collaborative leadership, partnership and structure

- Is the leadership and management strategy convincing and coherent?
- Does the consortium have sufficient critical mass, complementary skills and mix of disciplines?
- Is the expertise assembled appropriate and sufficient to answer the research questions?

Clarity and importance of vision and goals

- Does the vision of the Collaborative meet the call's remit and the nature of the challenges to be addressed?
- Have applicants demonstrated their research truly addresses multimorbidity and is there clarity in their concept/approach to multimorbidity?
- How does the research differ from what has been done previously and does it add to the evidence base in a way that can be built on in the future?
- Do the outcomes and proposed consortium approach have high potential to produce actionable evidence and to bring about demonstrable change for the future health and care system?

Scientific potential and feasibility

- Are the work packages coherent, fully justified, and aligned with the overall vision of the proposal?
- Are the proposed approach and methods appropriate to the research question?
- Are the research objectives achievable?
- Within the funding period of the consortium, will it provide new scientific knowledge and methodological learning?
- What level of innovation, including in methods development, will be achieved?

Data-readiness and management

Note: *Consolidator grant* applicants are likely to be at different stages of development of their data approaches and can use the awards to progress those. Groups applying directly for the *Research Collaborative awards* are expected to be able to demonstrate maturity of their data management plans. The funding Panel will be considering the likelihood that the data used and/or generated within an award can be successfully integrated into a nation-wide health data resource, based on the following questions:

- Do the applicants already have the data themselves or have made the necessary arrangements to obtain the data elsewhere?
- Do the terms of use of the data and approvals received match the requirements for the research proposed?
- Whether the data reside in the secure and trusted research environment (TRE) or this still needs to be developed?
- Will the applicants be dealing with a single or multiple TREs in their research?
- Do the involved datasets require linkage or have already been linked and can be readily used for the identified gap analysis?
- Whether strategies, procedures and processes for making the data accessible and discoverable to others are in place or need to be developed further?
- Whether the proposed overall data management approaches and plans are complementary to the health data infrastructure being developed in the UK?

Impact and Wider Applicability

- What is the health and care relevance and importance of the research; and is there a clear and reasonable statement of the practice implications in the application?
- Has the consortium demonstrated a clear path for translation, engagement with users and/or influence on policy and practice? Is the extent of co-production with patients and health and social care practitioners appropriate?
- Does the consortium subscribe to the plan to make data available and share learning with other funded projects?

Value for money of the proposed work

- Are the requested resources sufficiently justified and required to achieve the goals of the study?
- Are there any plans for to sustain the consortium beyond the tenure of the award?

Please note, applicants will be contacted via email after the panel meeting to inform them of the panel's decision. Panel decisions are final and there will be no opportunity to respond to the feedback though successful applicants for each category will be expected to address the feedback when implementing their *Consolidator grants* and /or when submitting the full application for the *Research Collaborative awards*.

7. Who can apply?

The following may apply:

- standard MRC eligibility rules apply as described in the [MRC Guidance for applicants](#)
- MRC unit/institute staff.

Public Sector Research Establishments (PSREs) are also eligible to apply to SPF programmes. If PSREs wishing to apply have not previously applied for UKRI funding and are not currently designated IRO status they will be required to complete an eligibility form to ensure they have the required research capacity, systems and controls in place to manage the research and grant funding. See <https://www.ukri.org/funding/how-to-apply/eligibility/> for further details and information how to become an eligible PSRE.

While the proposals can only be led by an eligible UK-based principal investigator, researchers from overseas institutions may be included in a proposal as a co-Investigator where this adds value to the research. Applicants will need to justify how overseas investigators/resources enhance the impact of research.

All investigators (PI & Co-Is) are required to have a verified Je-S account. Please note that opening a Je-S account can take some time, so applicants should start the process as soon as possible.

8. Applications involving industry

Applicants with an industrial partner(s) should follow the [MRC Industry Collaboration Agreement](#) (MICA) process and will need to submit a [MICA Form](#) and Heads of Terms at the time of the full Research Collaborative application. Industrial collaborators cannot be recipients of funding and must be listed as Project Partners. For more details please refer to the guidance on [MICAs](#).

Consolidator grant applicants, who develop proposals involving industry need to contact the Head Office sending an email to multimorbidity@mrc.ukri.org to discuss the role of their industry partner(s) at this stage.

9. Key Dates

Launch of call	11 November 2019
Closing date stage 1	11 February 2020 16:00 (GMT)
Funding decision on Consolidator grants and Research Collaborative award outlines by the Expert Review Panel	March/April 2020 (TBC)
Funding decision on the 1 st wave of Research Collaborative awards	Summer 2020 (TBC)
Funding decision on the 2 st wave of Research Collaborative awards	Early 2021 (TBC)

10. Contacts

Applicants may wish to discuss the suitability of their proposal for the remit of the call, or other questions related to the scientific aspects of their application sending a query to multimorbidity@mrc.ukri.org. Should applicants have any queries they wish to discuss over the telephone they are advised to contact Rachael Cartwright on 0179 416308 in the first instance.

To discuss your eligibility or any other non-scientific queries please contact our Research Funding Policy and Delivery Team: RFPD@mrc.ukri.org.

Queries relating to Je-S should be directed to the [Je-S Helpdesk](#).