Medical Research Council

Guidance for Outline Stage Experimental Medicine Applicants

OFFICIAL

Contents

Disclaimers

The information contained in this document is additional specific guidance for Experimental Medicine applicants, and should be used in conjunction with other MRC sources of information when preparing your application, for example:

- Experimental Medicine Call Webpage
- MRC Guidance for Applicants – details on eligibility, costings and responsibilities;
- MRC Industry Collaboration Agreement (MICA) – relevant to industrial collaborations;
- Je-S Help – for information or queries related to use of the Je-S System.

Please ensure you have downloaded the latest version of this document via the Experimental Medicine webpage.

Version 3.1
Jan 2022

Aims and Remit

The Experimental Medicine Panel will fund ambitious clinical studies to address gaps in our understanding of the causes, progression and treatment of human disease. These grants will produce new **mechanistic insights**, identifying opportunities to modify disease pathways and enabling novel therapeutic or diagnostic approaches for future development.

Applications must be:

- **Challenge-led**: Based around a clearly articulated gap in understanding of human pathophysiology with a clear path to clinical impact**. Applications should be centred around a strong mechanistic hypothesis.**

- **Human-focused**: The focus should be on understanding human disease through experimental investigation in humans. While projects may include a limited, well-justified element of non-human work (specifically to inform the proposed work in humans), **the main focus of the project should be on human participants**.

- **Ambitious and innovative**: Research proposals should address important medical questions in new ways.

- **Experiment-driven**: Proposals should be structured around an experiment designed to address a mechanistic question and identify clear outcomes that enhance our knowledge of, and provide confidence in, specific targets or pathways, therapeutics or technologies.

Experimental Medicine (EM) studies must involve an experimental intervention/challenge in humans, perturbing the system to explore disease mechanisms. The challenge may include, but need not be limited to, pharmacological, immunological, physiological, psychological or infectious modalities.

Applications that do not involve an experimental intervention or challenge in humans are ineligible for this funding scheme.

Proposals may include:

- The use of novel readouts or technologies related to early evaluation of clinical efficacy or pathogenic mechanism.
- The use of drugs, other interventions or measures with established safety profiles in new settings/conditions: e.g. repurposing drugs as tool compounds to probe disease mechanism.
- Characterisation/phenotyping of subjects using samples from clinical studies may be included where there is a clear link to a current treatment strategy but should not be the sole focus of the proposal. Limited, hypothesis-driven, retrospective sample analysis may be included at the start of the project to improve the design of the interventional, experimental medicine study. Milestone criteria should clearly detail what data are required from the confirmatory analysis for the project to progress.
- Prospective, nested studies within a larger cohort trial may be eligible provided they can demonstrate added value, are exploring disease mechanisms, test a novel hypothesis and address a different question to the main study.

Competitive proposals will aim to address a clear mechanistic question and provide strong rationale to justify the suitability of the experimental system proposed to test the presented hypothesis. Proposals which are predominantly descriptive will not be shortlisted.

The following activities are ineligible for support:

- Characterisation/ phenotyping work aiming to elucidate disease aetiology (supported by the Research Boards)
- Biomarker discovery (supported by the Research Boards)

- Experimental intervention/challenge in animals, using clinical assets to explore disease mechanisms and pathways (supported by the Research Boards)
- Development and evaluation of novel therapeutics, diagnostics or devices (supported by DPFS)
- The development of novel technologies without a clearly defined hypothesis-testing programme
- High-throughput screening approaches to target validation
- Pre-clinical model development and validation (supported by the Research Boards)
- Clinical efficacy trials (supported by the EME funding scheme)

Common failings in experimental medicine studies include:

- Excessively broad and all-inclusive 'omics' approaches, without sufficient rationale for the variables to be measured. As noted above, projects should include a novel and clear hypothesis and, particularly if biomarkers are employed, they should be utilised for the evaluation of mechanisms of disease or response.
- Unnecessarily high costs resulting from lack of focus – applicants should consider "what is the critical path?".
- Poor statistical justification for the sample size and study design, e.g. around effect size estimation. Studies should look at mechanistic study outcomes rather than clinical efficacy alone.
- Weak case for the importance of the work in the context of other studies in the area, and the potential impact of the mechanistic knowledge that will be gained. How will the insight gained be exploitable or developed further in subsequent studies?
- A lack of innovation in the methods and measures employed
- Unclear justification of how the challenge designed will allow mechanistic questions to be answered. Will the system or intervention proposed allow you to address the key study questions?

The Experimental Medicine Panel will support a range of award scales, from smaller, focussed, more exploratory and highly innovative projects (based e.g. on an intellectually sound hypothesis but perhaps lacking extensive pilot data), to larger scale awards based on a more substantial platform of data.

Outline Applications

Applicants must first submit an outline application. The purpose of the outline application is to ascertain whether the project's aims, rationale and deliverability are appropriate for consideration by the Experimental Medicine Panel.

To submit an outline application, the applicant must complete the Experimental Medicine Outline Case for Support Form and submit this as a PDF via the Je-S website.

The Experimental Medicine Outline Case for Support Form consists of eight sections. Use the tab key to move between cells in the form. Cells that are greyed out do not need to be filled in, since these are automatically calculated from cells elsewhere in the form.

A checklist of the compulsory and optional attachments that should be included in the application is provided at the end of this document.

Outline Application Assessment Criteria

Panel decisions at outline stage are to; Invite a full proposal or Reject the proposal (Decline). Should your outline proposal be Declined, you **cannot** re-submit the same or a similar application within 12 months of the original application deadline.

In exceptional circumstances, the Panel may give Positive Feedback, whereby the proposal is declined, but the 12-month moratorium on a re-submission is waived.

Please note that the decisions of the Experimental Medicine Panel will **not** be open to appeal, and that the MRC reserves the right to amend the application process.

Full proposals will be assessed on the standard criteria for an MRC research grant, in addition to the following Experimental Medicine criteria:

- **Fit to the call remit:**
  - Is the proposal within remit?

- **Rationale & potential impact:**
  - Proposals need a structured rationale for the mechanistic hypothesis to be defined and tested, and for the readouts and measures which are proposed.
  - Is there a strong scientific rationale for the project, supported by an appropriate level of evidence?
  - Does the proposal address an important, clearly-articulated and tractable gap in understanding?
  - Is the proposal likely to lead to improvements in understanding of human disease mechanisms?

- **Research strategy:**
  - Is an appropriate experimental scientific strategy presented to address the research question?
  - Have the investigators chosen a suitable range of approaches to deliver new insights, and do the individual strands of work reinforce each other?
  - Does the plan propose appropriate go/no-go milestones?
    - Are the milestone timings appropriate and are the success criteria necessary and sufficient to judge progression?

- **Quality and skills of the research team**:
  - Are these appropriate to deliver the proposed research?
  - Are the number and skills/experience of requested staff appropriate for the work described?
  - Have the applicants set out a clear and reasonable case for the requested levels of staffing?

- **Research environment & infrastructure**:
  - Is the required research and/or clinical infrastructure in place?
  - If appropriate for the proposed work, do the applicants plan to make use of Experimental Cancer Medicine Centres, NIHR's Biomedical Research Centres (BRCs), patient cohorts or other established infrastructure across the UK (not mandatory)?

- **Experimental design and statistical considerations**:
  - Studies should be methodologically and statistically rigorous in design and should take appropriate steps to minimise bias and have sufficient sample sizes to address the research questions. We acknowledge that performing a formal power calculation may not be possible, or preferable in some cases, but a clear scientific justification of the

sample size required to satisfactorily address the research question(s) is expected (e.g., to achieve a certain level of accuracy in parameter estimation).
    - If formal power calculations are possible, then please consider the following: Where the study has a mechanistic, rather than efficacy, focus, consider using 80% power or a higher false-positive error rate, i.e. 10 or 20% instead of 5%. In addition, consider whether a one-sided or two-sided test is appropriate.
    - Have the applicants described a clear experimental design with appropriate statistics/processes in place for the conduct and analysis of the research?
        - Is the sample size adequate to achieve the aims of the study from a statistical perspective?
        - Is the sample size reproducible?
        - Include a summary of study design, study participants, study endpoints, dose (when applicable), anticipated effect size/accuracy measures and analysis plans.
    - Are appropriate staff (e.g. a statistical co-applicant) involved to support this?

- **Risk mitigation & management**:
    - Projects that explore new areas will involve scientific risk that results are not as anticipated; the Experimental Medicine call can accommodate this. Are there appropriate plans in place for risk mitigation and management, including milestones?

- **Resources:**
    - Is the budget realistic for the scale and complexity of the project?
    - Are project costs that will be met by sources other than the MRC clearly identified?

Milestones

Milestones allow the MRC to mitigate risk and support potentially high-risk projects.

Experimental Medicine awards will typically have 2 Milestones with specific success criteria that reflect major progress points and allow mechanistic hypotheses to be laid out and evaluated as the project progresses.

The Milestones should also provide a realistic indication of timelines for key steps, such as regulatory steps, study team recruitment, participant recruitment, study completion and data analysis.

Milestone success criteria should be SMART (specific, measurable, achievable, relevant, timely), and detail any robust Go / No-Go criteria. For all projects, it is advisable to structure the project so that the critical question(s) are addressed as early as possible in the plan.

Partnerships and Industrial Collaborations

Applications including partnerships with charities or industry are encouraged where these add value to the project – for example, in terms of access to expertise, technologies, reagents or co-funding. Please note that industrial collaboration is not a prerequisite for application.

Applicants are encouraged, where appropriate, to make use of existing infrastructure across the UK for experimental medicine, e.g. Experimental Cancer Medicine Centres, the NIHR Biomedical Research Centres (BRCs), etc.

If the application involves an industrial partner, please refer to the MRC Industry Collaboration Agreement (MICA) webpage for further guidance.

Applications involving collaboration with industry should adhere to the MRC Industry Collaboration Agreement (MICA) guidance. The lead applicant must be the academic partner, and MRC will meet the academic costs of the project only.

A Letter of Support from the Project Partner is optional, but highly recommended at outline stage.

Intellectual Property

Note that the generation of protectable intellectual property is **not** an essential requirement for this scheme.

Intellectual property generated in the course of a project will (subject to the conditions of the MICA system) be owned by the host institution, which will have the right to manage and exploit this intellectual property.

You are encouraged to think broadly about the IP that will be developed during the project. In addition to patents and copyright, consider know-how, methods, algorithms, trademarks and data.

The costs of managing, protecting and exploiting the intellectual property are borne by the host institution and are not eligible costs for MRC support.

Costs and Duration

Please note that there is no formal limit to the total amount that can be requested in an Experimental Medicine grant – all costs should be fully justified within a proposal and the Panel will assess value for money in the context of the proposed work.

To allow the Panel to evaluate the value for money, please indicate what the entire project cost will be. The full economic cost (FEC) includes full academic costs and project partner contributions.

Please note that there is no formal expectation of the duration of Experimental Medicine grants. Project duration should be dictated by the timelines required to complete the proposed work, although this will usually be between 12-60 months.

Please include estimates of the duration and costs you anticipate will be required to reach each relevant checkpoint and any project partner contribution. The form in section 8 of the case for support will calculate the expected total project duration and full economic cost.

Additional guidance on Exceptions Costs can be found in the Outline Resource Summary section of Je-S, and in Section 3.2.5 of the MRC Guidance for Applicants.

Costs for subcontracts with contract ROs for the synthesis/manufacture of an entity or matched placebo carried out under Good Manufacturing Practice will be paid at 100% FEC. Please speak to the Programme Manager regarding any Exceptions Costs queries.

NHS Costs

Applications may include research costs associated with NHS studies, if appropriate. Please summarise the expected activities and costs, alongside justification to why/how these are necessary for the research proposed.

If you are applying for research grants that require NHS support or HRA approval, you will need to submit a completed Schedule of Events Cost Attribution Template (SoECAT) at the full application stage. This is not required at the outline stage.

Please refer to Section 3.5 of the MRC Guidance for Applicants for further guidance on NHS costs.

Compiling the Gantt Chart

A one-page Gantt Chart is required at outline stage, and should include:

- Project tasks (these being short, achievable and measurable activities) with, where relevant, the party responsible for delivering the task and dependency relationships between tasks; and
- At least two progression milestones (to include the project end goal), these being major specifically-timed decision points.

Once completed, the Gantt chart should be saved as a pdf file and submitted via the Je-S system under the document type “Gantt Chart”.

Ethics and Regulatory Approval

The MRC does not require ethics permissions and regulatory approvals to be in place when you submit an application (outline or full).

However, given that research involving human subjects or requiring the use of human tissue/organs may raise various ethical and regulatory issues, **applicants will be required to demonstrate that they have adequately considered these matters.**

Early discussions with regulatory bodies are advised to ensure that all requirements can be met in a timely manner. Once an application is successful, it is the responsibility of the host institution to ensure that the appropriate ethics and regulatory approval has been obtained and that no research requiring such approval is initiated before it has been granted.

Please read the MRC Additional Terms and Conditions for further details.

Support for Applicants

Applicants are strongly encouraged to engage with their institution's Research Governance Office who will be able to offer guidance and support.

Guidance is available on the MRC Regulatory Support Centre website, developed in collaboration with the Health Research Authority, for those conducting research with human participants, their tissues or data. Applicants are strongly encouraged to look at and make full use of The Experimental Medicine Tool Kit.

The vast majority of studies that involve human participants, their tissues or data should undergo a research ethics committee (REC) review and many research studies may require an NHS REC opinion. The HRA Decision Tool can be used to determine whether your study requires this type of approval.

The Integrated Research Application System (IRAS) should be used when applying for NHS REC approval and for other regulatory approvals. IRAS is a single system for applying for the permissions and approvals for health and social/community care research in the UK.

Prior to the establishment of the Experimental Medicine Panel, the MRC ran four ad hoc Experimental Medicine Challenge Grant calls. As part of these calls, a webinar was held to articulate the remit of the scheme, what qualifies good experimental medicine, challenges identified from previous rounds and how successful applications were designed, reviewed and conducted. Applicants may find this resource useful in preparing an Experimental Medicine proposal. A link to the webinar can be found here.

Using the Joint-electronic Submission System

The Joint Electronic Submissions (Je-S) Helpdesk is the first point of contact for the Research Councils.

If you experience difficulties using Je-S or have questions regarding its use, the helpdesk can be contacted on:

- Email: JeSHelp@je-s.ukri.org
- Phone: +44 (0) 1793 44 4164 *
- Staffed Monday to Thursday 8.30am - 5.00pm UK Time & Fridays 8.30am - 4.30pm UK time (excluding bank holidays and other holidays)
- Out of hours: leave a Voice Mail message

When reporting problems by e-mail or telephone, please supply the following information:

- Your name, organisation and User ID
- The date and time
- The part of the form or system you were working on when the problem occurred
- The nature of the problem

** Phone calls that cannot be answered during working hours will be redirected after 30 seconds to Voice Mail. The helpdesk will normally return your call within 3 hours.*

Board or Panel Portfolio: Experimental Medicine

Contacts

For general enquiries, please contact the Experimental Medicine team on experimental.medicine@mrc.ukri.org.

We encourage potential applicants to contact the Experimental Medicine team to arrange a discussion with the Programme Manager around remit suitability prior to submitting an application.

Checklist of Attachments

Attachment (in PDF format)	Attachment type on Je-S	Page limit or formatting
Mandatory		
Experimental Medicine Outline Case for Support Form	Case for Support	Experimental Medicine Outline Case for Support Form
CV for • Principal Investigator • Co-Investigator(s) • Researcher Co-Investigator(s) • Any named staff Please refer to Section 2.2 of the MRC Guidance for Applicants for further information on CV requirements.	C.V.	Up to 2 x A4 pages Font Arial, 11 point
Publication list for • Principal Investigator • Co-Investigator(s) • Researcher Co-Investigator(s) • Any named research staff Please refer to Section 2.2 of the MRC Guidance for Applicants for further information on requirements for publication lists.	List of Publications	1 x A4 page each Font Arial, 11 point
Gantt chart	Other Attachment	1 x A4 page
Supporting figures and data tables	Other Attachment	Up to 2 x A4 pages
Justification of resources Please refer to Section 2.2.4 of the MRC Guidance for Applicants for further information on JoR documents	Justification of Resources	2 x A4 page
Mandatory if applicable		
MICA Form if the project involves any industrial partners	Other Attachment	MICA Form
Optional (but highly recommended)		

Letter(s) of support from key collaborators or partners, such as industrial partners or clinical collaborators / recruiting centres	Other Attachment	Up to 2 x A4 pages each
Covering letter	Other Attachment	1 x A4 pages Font Arial, 11 point
Letter(s) of support if the project includes Researcher Co-Investigator(s) (RCo-I) The Principal Investigator should use this letter to highlight the support for the Researcher Co-Investigator(s) to further their career and personal development throughout the duration of the project. Please refer to Section 1.3.3 of the MRC Guidance for Applicants for further information on our expectations of support for Researcher Co-Investigators.	Other Attachment	Up to 2 x A4 pages each

Not accepted at outline

Anything not listed will be considered an ineligible attachment and will **not** be accepted (unless prior permission has been sought from your Programme Manager). These include, but are not limited, to:

- Heads of Terms
- Quotations (for equipment, subcontracted work, etc.)

Please note: the MRC reserves the right to decline or return an application on eligibility grounds, if documents other than those detailed above are submitted, or if the guidance indicated above is not adhered to. Failure to follow the guidance may prejudice your application.