 

**Full application guidelines – Translational Research Questions**

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**Introduction to full application guidelines for translational research questions**

This document is intended to act as a guide for applicants answering translational questions in the full application form. It outlines key points to consider when filling out each section of the form. Please use this guide in conjunction with pointers already provided in the full application form.

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Section 1: Further Applicant(s) Details

Please provide details of the additional contacts on the project using the existing format. Details should correspond to those provided in the submitted outline application.

Section 2: Need and Proposed Solution

Introduction to disease

* Please include information on typical disease progression

*What is the rare disease health, clinical or product need you are seeking to address?*

* Clearly state the target paediatric population, including specifics on age and genotype. For example, is the proposal focused on a subset of patients with specific pathological mutation?
* Do paediatric patients typically experience a diagnostic odyssey? At what stage of disease progression are paediatric patients typically diagnosed?

Explain the current standard of care and unmet medical need

* Briefly summarise the current treatments available for target paediatric patients. Are current treatments curative or do they only manage symptoms?
* Are target paediatric patients well served by current treatment, what are the key limitations of current treatment? Explain why there is an unmet need for target paediatric patients.
* What is the timeline for delivering the proposed intervention? Will there still be an unmet need by the time the proposed intervention is likely to be ready for delivery to patients or is it likely that other (competitive) approaches will have sufficiently addressed the unmet need by this point?

What is your proposed solution to this need and its advantages?

The proposed solution:

* Describe the proposed intervention and how it will address unmet need in the target paediatric rare disease.
* Is it acceptable to use the proposed intervention in a paediatric population?
* At the point of proposed intervention, what stage of disease progression will paediatric patients typically be at (eg., pre-symptomatic or post-symptomatic)?
* Will the proposed intervention be an adjunct to standard care or only as an alternative for patients who have failed conventional therapies?
* Is the proposed solution likely to be compatible with current clinical practice?
* A tabulated Target Product Profile (TPP) is highly encouraged to describe the proposed intervention as it will help explain the desired endpoint and should therefore capture what the proposed intervention needs to achieve. A robust TPP will also help with the design of milestone success criteria (see Section 3). Further guidance on formulating a TPP can be found in Appendix 1.

Advantages of the proposed solution:

* Additional questions applicants should consider when describing how the proposed intervention will be an improvement on existing solutions:
	+ Would meeting unmet need significantly reduce disease burden and/or provide a valuable commercial opportunity and/or alleviate an important development bottleneck?
	+ Could the proposed intervention or components thereof meet other significant needs (eg., proposed intervention applicable to other indications)?
* Applicants could consider listing distinct advantages of their proposed intervention. As an example, advantages of a drug discovery project could include:
	+ Why the proposed drug target is attractive – tractable target for treatment of disease, accessibility to proposed drug modality (eg., cell surface expressed CNS ion channel accessible to small molecule capable of BBB penetrance), target easily druggable.
	+ How the proposed administration route is an improvement on existing delivery and/or the most preferred and convenient route of administration for paediatric patients. How proposed administration route may allow topical delivery to affected tissue to enable higher dosing whilst avoiding side effects from systematic administration.
	+ How the proposed intervention will avoid side effects. For example, drug target is highly and selectively expressed in disease affected tissues/cells and project aims to develop highly selective modulator of drug target. Support from genetic knock-out or pharmacological studies with tool compounds that show absence of side effects or toxicity.
	+ How acquired data support a disease-causing role for the drug target (eg., genetic or functional data). This should be brief (1-2 lines) and covered in more depth in Section 3.
	+ Stating that applicants have developed or are in possession of key assays and/or models that will enable project delivery. This should be kept to a few key examples and covered in more depth in Section 4.

Strategic position

* What is the development stage of competing strategies? Highly promising competing strategies or those in clinical development should be given higher priority and described in greater detail (limiting to key points). Describe how you have identified competing solutions.
* If applicable, consider grouping relevant competing strategies into common modalities.
* Have any competing solutions reached regulatory approval? If applicable, state why competing solutions have failed in clinical trials and how the proposed intervention may avoid previous failures.
* Would the proposed solution, if achieved, be widely adopted? If the anticipated cost for the proposed intervention is higher than for competing solutions, the need for extra spending will need to be justified (to NICE downstream).

Section 3: Description of Proposed Project

Scientific background

* A brief description of background studies should be provided alongside a key summary of current progress and supporting evidence generated by the applicant. This summary should provide sufficient details of past and current research to show that project aims are scientifically justified. Examples of supporting background evidence/data could include genetic evidence, functional/proof-of-concept and/or pharmacological studies.
* Full references can be provided as an annex to the application form (one page maximum).

List the objectives/milestones of the proposed project.

* Objectives, and particularly milestones, are a common weakness in proposals because they lack sufficient detail and/or structure. Funded projects are required to report quarterly and may be stopped if they fail to meet pre-agreed milestone criteria, hence proper milestone construction is important.
* Objectives are the main aims or goals - the anticipated outputs of the proposed work. These are distinct from milestones, which represent key work packages in the overall programme of work.
* Milestones should be SMART (Smart, Measurable, Achievable, Relevant and Time-bound), logically build (ie., previous milestone provides sufficient data/evidence to progress to the next), and reflect key go/no-go decision points on the path to project endpoint and/or longer-term goals. Further guidance on milestones can be found in Appendix 2.
* In describing milestones, please provide the timing and duration of the milestone and details of success criteria. Project plans typically contain between 2-3 Milestones, with one corresponding to project end.

Experimental design

* Please explain how you will achieve the aims set out in objectives, including a brief description of assays/experimental work and why you will be performing them.
* When providing statistical justification, explain how calculations were performed and the background data and/or assumptions used. If appropriate, include an explanation of how studies will be randomised and/or blinded.
* For projects planning extensive animal work, it is encouraged that applicants tabulate the total number of animals to be used (see table below as an example). This provides a useful summary and will help justify animal numbers alongside statistical justification.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Objective 2.1 | Objective 2.3 | Objective 4 |
| Type of experiment | Modulation of ion channel synaptic transmission in cerebellar slices |  |  |
| Data (ie., data obtained from animal experiments) | Electrophysiology data |  |  |
| Sample size (statistically justified) | 7 |  |  |
| Experimental conditions (eg., genotype) | WT and target knock-out+/- compound |  |  |
| Total number of mice | (6 x 2) x 2(Sample size x Experimental condition x +/- compound) |  |  |
| Reference for animal model (PMID number) if applicable |  |  |  |

Section 4: Deliverability

Describe the stages of the project, associated risks, how likely these risks are to occur and how the risks will be mitigated.

* Applicants may not know the exact route their project will take but they need to be able to show how they will decide how they will get to the desired outcome (milestones/project endpoint).
* Applicants could consider using a diagrammatic flow-chart to illustrate and describe the stages of the project. The flow-chart should include:
	+ Project start point.
	+ Key stages of the project split up into objectives
	+ Key no/go decision points
	+ Contingencies plans/stages and could include interdependencies if the project contains more than one major workflow.
* Use of a Gantt to illustrate timelines, milestones (including objectives that will build towards milestones) and an overview of how the project will be delivered is highly encouraged. An example of a Gantt chart with sufficient detail for a 2 year project is provided below, although applicants should tailor Gantt chart design to their own project.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Yr 1 | Yr 2 |
| Objective | Milestone summary | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| 1.1 | Description of Milestone |  |  |  |  |  |  |  |  |
| 1.2 |  |  |  |  |  |  |  |  |  |
| 2.1 |  |  |  |  |  |  |  |  |  |
| 2.2 |  |  |  |  |  |  |  |  |  |
| 2.3 |  |  |  |  |  |  |  |  |  |
| 3.1 |  |  |  |  |  |  |  |  |  |

* Please organise risks/mitigation strategies by objectives. Applicants should state any key risks to each objective, how likely risks are to occur, the impact of the risk on the project, and provide an explanation of how they aim to mitigate risk.
* Aim to manage risk across the duration of the project as too many uncertainties associated with any given step may reduce confidence in the overall project feasibility. An example of risk description/mitigation strategy is provided below:

***Objective 1*** *– Medicinal chemistry to increase potency and CNS penetrability.*

***Risk*** *– Inability to generate compounds with sufficient Blood Brain Barrier (BBB) penetrance.*

***Mitigation strategy*** *– Applicants will perform in vitro potency and ADME assays upfront in objective 1.2. Based on target/acceptable values set out in the pre-determined TPP, applicants will only progress compounds with suitably improved potency, ADME profile and predicted BBB score. Applicants have two, structurally different chemical starting points around which to design new chemical series. If applicants observe no improvement in BBB penetrance in the first series, they will switch to the alternative second series. Applicants have previous MedChem experience in optimising small molecule compounds for BBB penetrance.*

* What resources/skills sets are required to deliver the project and how will they be obtained? Please provide a full justification for all salaried posts and expenses sought. In answering this question, please consider the following:
	+ Have you identified and secured reasonable access to the key resources/skills required to deliver the project? Is there likely to be a delay in project commencement until resources are in place?
	+ For PIs, is the requested time consistent with their proposed involvement, necessary or sufficient for the successful management of the research, and a realistic expectation of the time they could make available?
	+ Are the number and skills/experience of requested staff appropriate for the work described?
	+ Have you set out set out a clear and reasonable case for the requested levels of staffing and overall resources?
	+ Please elaborate on why the group is well qualified to manage the proposed project. Does the team have experience in delivering similar work packages in the past?
	+ Taking into account the expected benefits of the work proposed and the level of resources requested, does the proposal promise good value for money?

Section 5: Intellectual Property

Does the proposal and the onward development have freedom to operate or does it require access to background IP? If access is required, what IP does the proposal need access to? Detail institutions or individuals holding relevant background IP.

In answering these questions, the applicant should consider the following:

* What are the core technologies for the project – those that will be directly developed in the project?
* What are the most important tools (materials, methods and data) that will be used in the project but will not form a part of the project end result (delivery technologies). Examples of a delivery technology in the case of a drug-screening project could be the screening assay, substrate, and cell lines. Applicants would need to ensure they have rights to use these delivery technologies to perform the drug screen.
* Work with your Technology Transfer Contact to perform a prior art search that will identify relevant background IP. Hits identified in this search should give an indication on freedom-to-operate (FTO) issues, uniqueness of the core technology (evidence of how crowded the field is) and an indication on patentability. In performing this search, have all types of IP been considered that may be relevant to the core technologies?
* Seek your Technology Transfer Contact’s opinion on whether the project has FTO and the right to work on core technologies and use delivery technologies.

If access to background IP held by any third party is required, has access been agreed? If not, why do you believe you will be able to access the required IP on reasonable terms?

* In cases where the answer is “YES” (rights have been secured to core and/or delivery technologies), explain by what mechanism. For example, the applicant’s employer/institution owns the core/delivery technologies, has a licence to use core/delivery technologies for purpose of this project, has a Material Transfer Agreement to access core/delivery technologies, or has purchased delivery technologies (ensuring that terms and conditions of purchase do not restrict onwards exploitation).
* If the answer to this question is “NO”, please indicate who owns the core/delivery technologies. Describe why such rights have yet to be secured, what is the strategy to acquire them, at what stage the applicant is in negotiations for such rights, and when you expect the rights will be with the applicant.

What new IP or knowledge is the project expected to produce?

* Please consider all types of IP (patents, copyright, design, trademark, know-how, data).
* Is the IP generated in the course of the project likely to be protectable (i.e. will it be novel, non-obvious and useable)? Work with your Technology Transfer Contact to answer this question and consider seeking external patent attorney opinion on patentability if deemed appropriate.

How will project generated IP be managed and exploited to support the project in meeting its targeted need? Detail the organisations/individuals who will own any arising IP and any live, pending or envisioned agreements governing management or exploitation of that IP.

* Will the proposed management and exploitation strategy maximize the likelihood that the project will be able to access any required downstream funding to enable the project to meet its identified need?

Competitive landscape

* Is the competitive landscape crowded? Explain major competing solutions in more detail (compared to strategic position in section 2). Describe how you have identified competing solutions (if you haven’t already in section 2).
* What is the development stage of major competing strategies? Highly promising competing strategies or those in clinical development should be given higher priority and described in greater detail (limiting to key points).
* Have any competing solutions reached regulatory approval? If applicable, state why competing solutions have failed in clinical trials and how the proposed approach may avoid previous failures.
* Can the proposed approach map onto previous solutions that have already reached regulatory approval and/or clinical trials? Is this likely to smooth the route to patient delivery for the proposed approach (ie., other similar solutions have already navigated regulatory stipulations and issues with clinical trial design)?
* Have competing solutions attracted commercial interest? If yes, does this impact the likelihood of the proposed approach receiving downstream commercial support?

Section 6: Exploitation of the Project Deliverable(s)

Please describe your plans and strategy for further development of the project outputs? What are the obvious follow-on studies you will need to conduct in order to bring the proposed approach closer to patient delivery?

* What are the key steps that need to be achieved after project completion that will drive the project towards patient delivery/clinical trials (eg., development of a clinical therapeutic candidate that meets the appropriate safety, selectivity and efficacy profile to be used in the clinic by conducting follow-on *in vivo* efficacy, biodistribution and GLP/GMP toxicity and safety studies in an appropriate disease model).
* If appropriate, have applicants engaged with the MHRA to understand what is required to achieve regulatory approval?
* Are foreseeable downstream development hurdles surmountable? How will applicants overcome these hurdles?
* Will proposed work enable applicants:
	1. To conduct important follow-on studies that are necessary for progression towards clinical trial and patient delivery?
	2. To overcome downstream development hurdles?

How is the project going to be supported after the end of the project? List potential sources of further funding and comment upon the project’s compatibility with the individual fund’s defined remits.

* Description of downstream support is a common weakness in proposals because applicants fail to provide sufficient detail and/or the proposed strategy for downstream support is unrealistic.
* This is particularly important for this funding call as projects are often in the early stages of development with respect to translation.
* Applicants should therefore provide confidence that they have a reasonable plan for supporting the project after funding is completed.
* When listing potential commercial partners please consider whether partners would be appropriate to supporting the project – do they have an interest in the paediatric disease area and/or modality of proposed intervention?

Route to market

* What is the data package you will need to generate before licensing is considered? How far away is the project from generating this data package?
* Is there any evidence of commercial interest (eg., from competing solutions, see Section 5) in the target paediatric disease area and/or proposed therapeutic solution/modality that would indicate whether project is likely to receive downstream commercial support?
* If exit strategy does not involve commercial partnering and/or licensing, please explain how delivery to patient will be achieved.
* Is there a defined regulatory route for the proposed intervention or is there likely to be a need for a more bespoke regulatory pathway (eg., have similar therapeutic solutions already defined the regulatory pathway, see Section 5)? Outline the likely regulatory pathway, including time frame.
* How will applicants engage with patient advocacy groups and/or clinicians to ensure that downstream late-stage pre-clinical studies or clinical trials are appropriately designed to develop an intervention that meets paediatric patient unmet need.
* Will you require a CRO to perform specialised work in downstream development?

Are there any existing or potential restrictions on exploitation of the project objectives(s)?

* Please list any arrangements you may have with third parties that might limit the freedom of exploitation of IP generated by the project. These could be restrictions imposed by collaborators or sub-contractors, pipeline agreements, restrictions imposed by the owner of the core technologies, etc.
* If applicable, please describe what restrictions are and how these will affect your exploitation strategy.

Section 7: Miscellaneous

Previous funding

* Please list all sources of previous funding that have supported this project, including PhD studentships.

Miscellaneous

* The application form is designed to capture all relevant information, but all projects are different. Please use this section to provide any further information that ought to be considered by the panel.

Please scroll down for more information

Appendix 1: Guidance on Target Product Profile (TPP)

* A TPP is typically a set of 8-10 characteristics that the final intervention requires, including measurable performance values. Each TPP characteristic typically has two measurable performance values assigned, which are defined by:
	1. A quantified ideal/target value - the value that you are seeking to attain.
	2. A quantified acceptable value - the value that, if achieved, would support project progression.
* Applicants should consider whether TPP characteristics are likely to be clinically meaningful as this will affect the likelihood of successfully translating the intervention into the clinic.
* Further guidance on therapeutic and diagnostic TPPs, including examples, can be found at [Drugs for Neglected Diseases *initiative*](https://www.dndi.org/diseases-projects/target-product-profiles/) (DNDi).

*Suggested considerations for a therapeutic TPP:*

* Potency in *in vitro* assays and if relevant, *ex vivo* (eg., tissue sample) or *in vivo* (efficacy) tests.
* Selectivity (eg., against target homologues) in *in vitro* or *ex vivo* assays.
* Physiochemical properties (such as Mw, logD) which may guide therapeutic design.
* *In vitro* ADMET properties (such solubility, microsomal stability, Caco-2 flux, hERG) which may guide progression into *in vivo* testing.
* *In vivo* PK/PD.
* Further physiochemical or PK issues may need consideration in the TPP, such as CNS/BBB penetration required, multiple membranes permeability (eg., bacterial cell wall), must have short half-life, must be rapid onset, must be orally bioavailable.
* Suggested route of administration to paediatric patient, drug formulation and dosing frequency (how often, how long, amount?).
* Side effects – what would be acceptable in a paediatric patient population given the severity of the target indication?
* Suggested cost.
* Suggested time to patient delivery (how long will it take to develop before reaching patients?).

*Further considerations applicants may want to consider when drafting a TPP for advanced (cell and gene) therapies:*

* Alternative toxicity considerations (eg., immunogenicity or genotoxicity) and how these will be measured. If repeat dosing is likely, has immunological response been considered?
* Are novel routes of administration required, such as specialised surgical techniques, and are these available to paediatric patients?
* Will specialised formulation be required?
* Would concomitant medication be required, such as immunosuppressants, and can these be used in a paediatric population?

Further guidance on advanced therapy TPPs can be found at [CBER Office of Cellular, Tissue and Gene Therapies (OCTGT)](http://fda.yorkcast.com/webcast/Play/a53d0d5863244464b000249f1ddc9fd31d).

*Suggested considerations for a diagnostic TPP:*

* What is the ultimate goal of the diagnostic and intended use? Detection of infection or risk factor, companion diagnostic to therapy, prognosis?
* Who will be the target operator of the diagnostic?
* What is the minimum infrastructure required to implement the diagnostic test?
* What will be the format (eg., ultimate development of a kit, procedure, guidelines, App)?
* What is the target analyte/data/read-out to be detected?
* Target sensitivity and specificity (%s) in *in vitro* or *ex vivo* assays, and if applicable, in *in vivo* tests.
* If applicable, species differentiation (minimal requirement may be differentiation between genera).
* Qualitative or quantitative analysis? For example, detecting infectious agent burden may be qualitative, whilst a companion diagnostic for a therapy targeting an infectious agent may need to be quantitative?
* Sample type (eg., blood, urine, tissue sample, patient records)?
* If applicable, suggest the ultimate number of steps the diagnostic is likely to involve as an indication of the complexity of the test.
* Time to result (how quickly could diagnosis be performed)?
* Safety or side effects? Will diagnosis be invasive and will this be acceptable in a paediatric population. Will diagnosis require specialised techniques (eg., surgical procedures) and are these available to a paediatric patient?
* Suggested cost?

Appendix 2: Guidance on formulating Milestones

* Applicants should consider whether milestone timings and success criteria are reasonable and sufficient to judge project progression.
* Each success criterion is typically defined by (these could marry with TPP measurable performance values):
	1. A quantified ideal/target value - the value that you are seeking to attain.
	2. A quantified acceptable value - the value that, if achieved, would support project progression.
* Where appropriate, applicants should reference to the TPP to explain quantitative target and/or acceptable values for each success criterion.
* Applicants should also justify success criteria for the selected target and acceptable values. For example, in developing a diagnostic assay applicants might propose evaluating the assay’s Method Detection Limit (MDL) in whole blood as a criterion for one of the project milestones, using a target value of 0.02 ng per ml and an acceptable value of 0.04 ng per ml as set out in the TPP table (section 2). In this case, applicants should justify why the MDL is a suitable measure and why a limit of 0.04 ng per ml or less would support project progression.