Advanced Research + Invention Agency ARIA

Synthetic plants

Call for proposals

Date: 4 September 2024

v1.0

Advanced Research + Invention Agency ARIA

SECTION 1: Programme Thesis and Overview

This solicitation is derived from the programme thesis Synthetic plants for a sustainable future, in turn derived from the ARIA Opportunity Space: Programmable Plants - A technology platform for sustainable abundance.

The goal of this programme is to establish synthetic genetic units in crop plants. Plants with fully synthetic genomes could deliver an abundance of products and services sustainably, from food to materials, medicine, and beyond. A critical first step towards synthetic plant genomes is developing the building blocks: establishing synthetic genetic units, **specifically synthetic chromosomes and synthetic chloroplasts**, in plant cells. This programme aims to design, build, deliver and maintain synthetic chromosomes and synthetic chloroplasts that are viable in a living plant. A successful programme would not just demonstrate a critical step on the path to fully synthetic plant genomes, but would itself enable our major crops to be more productive, resilient and sustainable. This programme will unite expertise in synthetic biology and plant biology to catalyse the next generation of plant synthetic biology, unlocking new capabilities of plants to meet the future needs of humankind.

Key definitions

Synthetic chromosome – a nuclear chromosome composed of nucleic acids, that has been artificially synthesised *de novo* rather than assembled naturally. In this document, 'synthetic chromosome' refers exclusively to bottom-up synthetic chromosomes i.e. totally synthetic chromosomes; it does not refer to top-down synthetic chromosomes which are made by altering existing chromosomes.

Synthetic chloroplast – a chloroplast that has a fully synthetic genome (a genome that is artificially synthesised rather than assembled naturally). The chloroplast is not necessarily entirely synthetic (i.e. the chloroplast itself does not need to be assembled artificially rather than naturally).

Synthetic genome – a genome that has been artificially synthesised rather than assembled naturally.

Synthetic unit (or synthetic genetic unit) – refers to either a synthetic chromosome or synthetic chloroplast. This term is used throughout this document for the sake of conciseness.

Background

Plants are the foundation of our food system, and are indispensable providers of fuels, fibres and pharmaceuticals. Representing 450 gigatons of global carbon, plants are a critical and underutilised lever for solving the combined challenges of climate change and food security.

Synthetic biology can open up extraordinary new possibilities for plants. Synthetic biology is revolutionising the world of biomanufacturing and healthcare with novel approaches to drug production, CRISPR therapeutic treatments and the advent of personalised medicine. The applications of synthetic biology have focused on healthcare rather than agriculture, yet synthetic biology has the potential to transform the agricultural industry – an enormous global market predicted to amount to over £3 trillion gross production value in 2024. This presents a huge opportunity, considering the diversity of services provided by plants and the scope for impact from food to pharmaceuticals and beyond.

Within synthetic biology, synthetic genomes offer multiple benefits. They allow the creation of novel compounds and molecules that can act as pharmaceuticals and building materials that can be grown in plants rather than synthesised in a lab. They enable the development of organisms that are new-to-nature and capable of thriving in future climates or even mitigating climate change. For example, synthetic photosynthetic pathways can be used to dramatically increase carbon capture.

Compared to genome editing, the writing of fully synthetic genomes can include codon compression and expansion, leading to a new genetic code which is able to fulfil novel functions more readily. By using a new genetic code, genetic isolation is also possible, providing in-built biocontainment. Minimal genomes can provide reduced complexity, lower energetic costs and greater biosynthetic capacity. This programme will generate the building blocks needed for creating synthetic plant genomes in the future.

There are many challenges to overcome in assembling and delivering synthetic genome elements, such as chromosomes, into plants. Synthetic yeast and human chromosomes are being developed, and a synthetic chromosome fragment has been introduced into moss, but the development of functional synthetic chromosomes or chloroplasts delivered into higher plants including crops is still on the horizon due to the under-investment into plant synthetic biology compared with other areas of life sciences. This is partly caused by the

challenges of working with plants compared to other organisms, such as underdeveloped transformation protocols and long generation times. This programme will generate novel transformation methods to turbocharge the field of plant genomics and will leverage advances in plant biology, synthetic biology and genetics. We'll develop synthetic genomics in crop plants, using a diversity of disciplines to generate and test novel solutions on the journey to synthetic plant genomes. Recent advances in chromosome and chloroplast engineering mean that the time is ripe for a concerted effort across disciplines and approaches: to develop synthetic plant components delivering valuable benefits and ultimately enabling us to move towards synthetic plant genomes that enable new-to-nature capabilities.

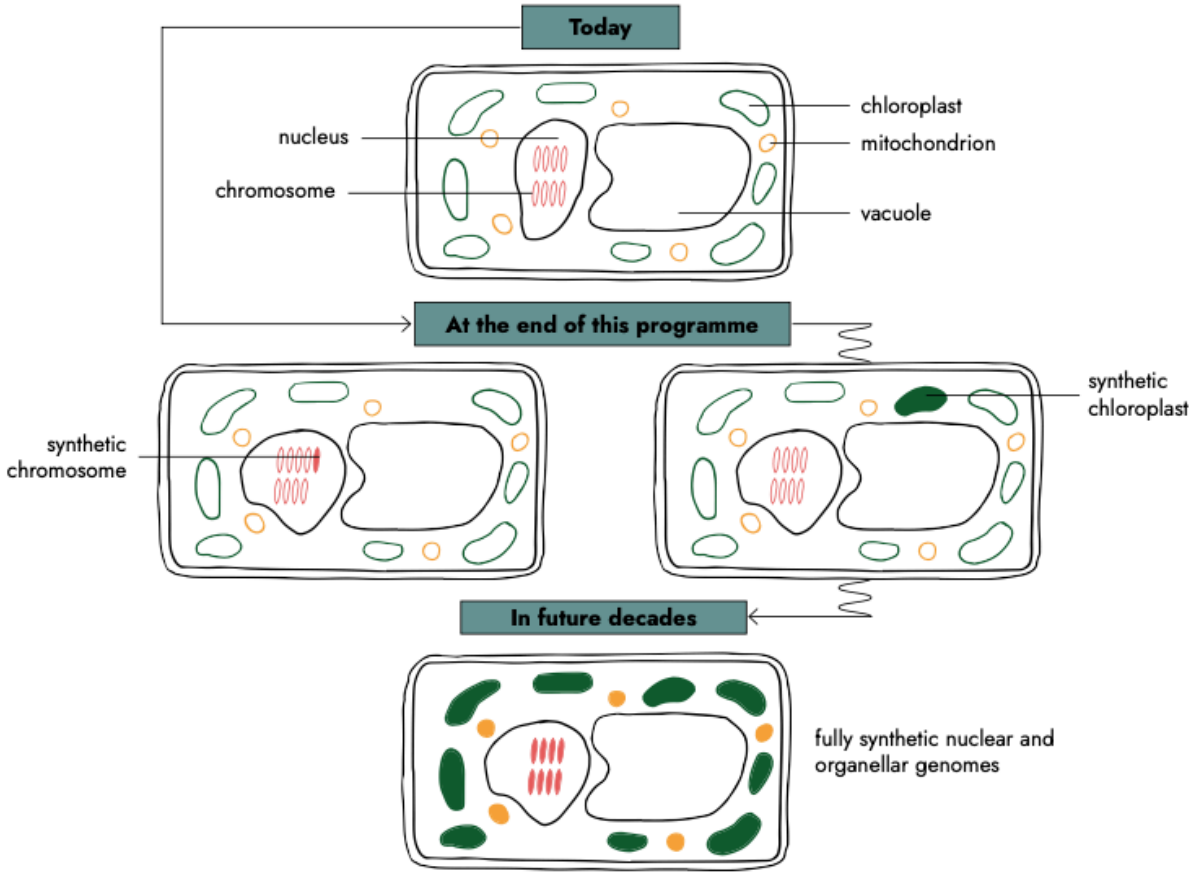
Our outlook

Success in this programme will enable us to move beyond what can be accomplished with gene editing, empowering us to imbue plants with entirely new suites of functionality. We expect to see technical innovations in the assembly of synthetic units, delivery of genetic material into plant cells, recoding of plant genes, advanced multicellular synthetic genetics and functional breakthroughs in crop traits.

The initial intrinsic value unlocked by this programme will be the generation of synthetic units that can be integrated into plants to introduce rationally designed functionalities that are valuable in their own right.

We expect that demonstrating that a functioning synthetic unit is possible will pave the way for progress in future decades: the development of a greater number and diversity of synthetic units delivering a wider range of benefits beyond those developed in the programme; the development of fully synthetic genomes in plants; and the delivery of new-to-nature capabilities.

For more detail on synthetic chromosomes and synthetic chloroplasts, refer to Appendix I in the Programme Thesis *Synthetic plants for a sustainable future*.


Today
nucleus
chromosome
chloroplast
mitochondrion
vacuole
At the end of this programme
synthetic chromosome
synthetic chloroplast
In future decades
fully synthetic nuclear and organellar genomes

SECTION 2: Programme Objectives

The goal of this programme is to establish synthetic genetic units (specifically, synthetic chromosomes and synthetic chloroplasts) in crop plants. The overall metric of success for this programme is that a synthetic unit functions and is maintained in three major crop species, delivering a complex trait that could not readily be introduced otherwise.

This programme has five Technical Areas (TAs), outlined below. This programme is structured in two phases: Phase One (TAs 1-2, over years 1-3) and Phase Two (TAs 3-5, over years 4-5). More detail on programme structure, and the scope of each Phase, is provided below ("Programme Structure"). **This solicitation is for applications to Phase One**.

Technical Areas

This programme has five technical areas (TAs). TAs 1, 3, 4, and 5 relate to the development of synthetic units. TA2 encompasses socioethical work related to the synthetic units. Refer to the section on "Programme Structure" below for detail of how the TAs are distributed throughout the duration of the programme.

'Synthetic unit' refers to either a synthetic chromosome or a synthetic chloroplast.

TA1: Design, Build, Deliver

- **TA1.1 Design.** Design the synthetic unit: develop design options, refine designs based on progress in Build and Deliver, and develop biological switches to turn the unit on and off *in vivo* (including a consideration of nuclear genes, for synthetic chloroplasts, and including consideration of recoded genome approaches for genetic isolation).
- **TA1.2 Build.** Build the synthetic unit: synthesise and assemble large pieces of DNA, test physical viability of the designed unit, and build units *in vitro* and *in vivo*.
- **TA1.3 Deliver.** Deliver the synthetic unit into plant cells: develop delivery methods for entire units or for components of units that can be assembled inside cells, achieve assembly of components of units inside cells if applicable, and develop selection procedure for transformed organisms. During the early stages of Phase One, a range of possible delivery techniques for both synthetic chromosomes and synthetic chloroplasts will be tested, and the potential for cross-species transferability

will be assessed. Delivery techniques with the highest potential for cross-species transferability will be selected as the focus methods for the remainder of Phase One.

TA2: Social and Ethical. Understand opinions and concerns of diverse stakeholders from different sectors, and review ethical issues around synthetic plants. This will include, but is not limited to:

- Studies of the possible opportunities and projected implications of synthetic plants (including advantages and disadvantages) for a range of stakeholders including farmers, industry supply chains, governance stakeholders and public
- Review of ethical issues around synthetic plants
- Public engagement to understand public opinion on synthetic plants and engage with public concerns, including understanding which of the proposed benefits of synthetic plants are considered credible and acceptable, and under which circumstances

TA3: Maintain. Demonstrate that the unit is maintained in plant cells after division: determine and develop what is necessary for ensuring maintenance and replication of the unit within the cell, test the functionality of the unit within the cell, and develop biological containment methods for the unit. Key tasks for TA3 include considering what is necessary for maintenance and replication of the unit within the cell, and prototyping in this area; ensuring maintenance and replication of the unit within the cell; testing the functionality of the unit within the cell; and developing appropriate biological containment methods for the unit.

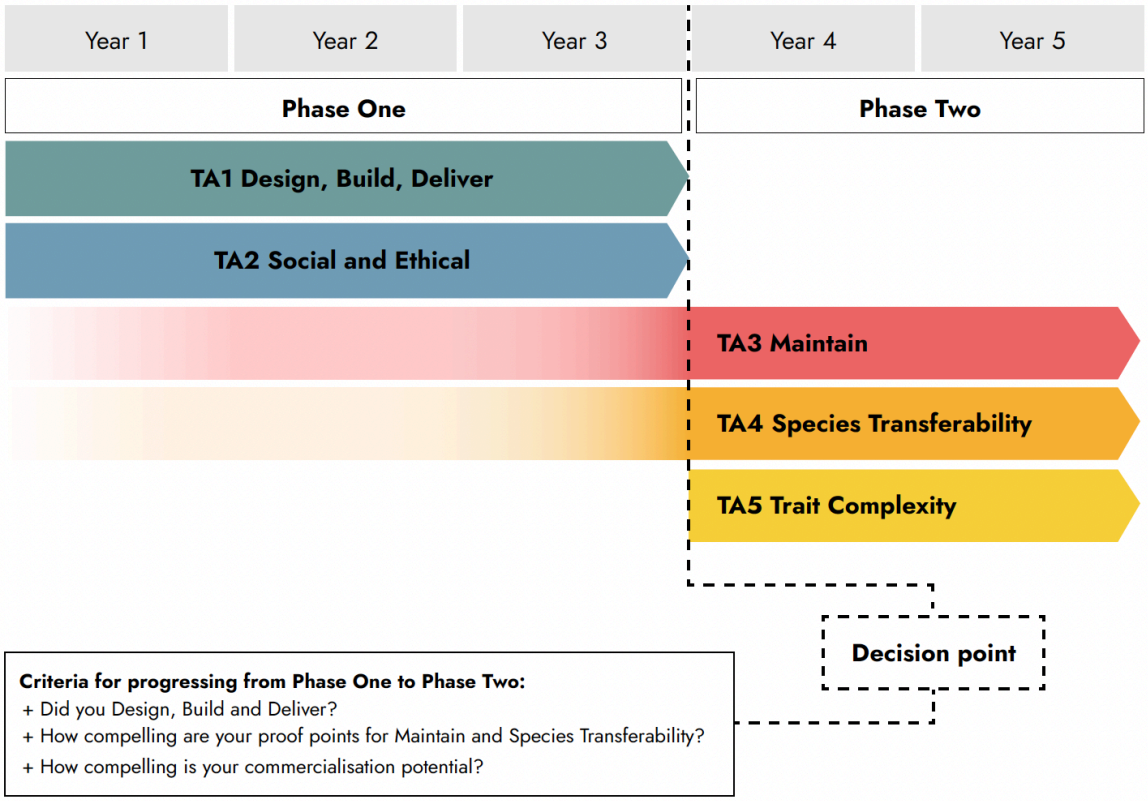
TA4: Species Transferability. Demonstrate that the unit or versions of the unit can be delivered into, and function in, multiple crop species including a monocot.

TA5: Trait Complexity. Deliver an agriculturally relevant complex trait using the unit. The specific trait is yet to be determined; traits related to food security will be favoured. The specific trait to be delivered will be based on the results of TA2 and/or on Creator expertise and preferences, in discussion with the Programme Director.

Programme Structure

Phase One will consist of work in TA1 and TA2. Teams from Phase One who have completed work on TA1 will be given the opportunity to work on at least one of the remaining technical

areas: TA3, TA4, and TA5. Additionally, depending on the progress and findings of TA2 during Phase One, there may be a decision point to extend TA2 work into Phase Two.



Progression to Phase Two of the programme depends upon successful completion of the Phase One TAs, along with proof points towards TA3 and/or TA4 based on initial proof-of-concept work in those areas carried out during Phase One. No proof points towards TA5 are required. Additionally, the potential to scale or translate into applications, for example by the creation of a spin-out company or a collaboration between different sectors, will be considered when progressing teams from Phase One to Phase Two. In order to progress, teams will be required to submit a proposal for their work in Phase Two. All funded Creator teams will have the opportunity to submit a proposal for Phase Two. There is also the possibility of assembling new Creator teams for Phase Two, composed of members of the teams in Phase One; we do not plan to issue a new funding call for Phase Two.

Applicants to Phase One of the programme are encouraged to include a brief section in their application detailing their approach to the work in Phase Two (up to 3 of TAs 3-5). However, this is not essential.

Traits

Applicants are free to propose any trait they wish to work on in Phase One. When moving to Phase Two, traits must be agriculturally relevant.

Species

To maximise the potential for the sharing of technical advances, work in Phase One will focus on a single crop species, potato (*Solanum tuberosum*) with expansion to additional species (including a monocot) in Phase Two. Potato has been selected for both social and scientific reasons: it is a crop of social and economic importance, and it is comparatively easy to transform. The specific variety of potato to be used will be determined in consultation with all Creators at the beginning of the programme. Proof-of-concept work during Phase One may be established in model species such as *Chlamydomonas, Physcomitrella, Lemna, Arabidopsis* or *Nicotiana*. We expect to see results in potato within 3 years. If establishing proof-of-concept work in model species in the first instance, we expect to see results in model species within 2 years prior to results in potato. When moving to Phase Two, further species should be selected with a view to maximising global societal impact and benefit to the UK.

Teams

In Phase One, each Creator team working on TA1 will work on all three elements within the TA (TA1.1: design; TA1.2: build; TA1.3: deliver). Individuals or teams with expertise in only some of these elements, or with experience in only one sector, are encouraged to form teams using the teaming tool, to form a team with overall expertise in TA1 and experience across multiple sectors.

For TA1, we expect teams to consist of collaborations between multiple groups of individuals, and we expect some teams of varying sizes.

We are more interested in research quality than team size. For both TA1 and TA2, we may decide to fund a larger number of smaller teams than indicated in this document (refer to the "Budget" sub-section below). Therefore, applications for smaller projects are welcome.

Budget

We expect to allocate £62.4m across this programme (TA1-TA5). In Phase One, we expect to allocate £44.5m across 9 Creator teams, as outlined in the following table.

Technical Area	Expected Budget	Expected Teams
TA1	£41.4m	6
TA2	£3.1m	3

SECTION 3: Technical Metrics

Each individual technical area (TA) will have the following metrics of success. The metrics reflect ideal milestones that should be reached but we appreciate the nature of research and encourage you to still apply if you think you could produce results that could relate to the desired metrics.

Technical Area	Metrics of success
TA1 Design, Build, Deliver	TA1.1 Design + Unit design delivers specified trait + Unit activity is regulated *in vivo* with at least the same level of nuance as in a natural occurrence of the trait TA1.2: Build + Unit is viable *in vitro* + Unit is viable and functional *in vivo* with at least the same level of functionality as in a natural occurrence of the trait TA1.3 Deliver + For synthetic chromosomes: delivery of 1 Mb DNA into cell

	+ For synthetic chloroplasts: delivery of 100-150 kb DNA into chloroplast within cell + Unit can be inserted into or assembled inside cells with >5% success rate + Transformed organisms can be selected rapidly and accurately, with a greater throughput for identifying transformants than is currently possible in tissue culture
TA2 Social and Ethical	+ Diverse stakeholders engaged + Ethics roundtable held and outcomes published in public domain + 5 public engagement activities carried out (including surveys and workshops)
TA3 Maintain	+ Unit replicates inside the cell + Unit remains stable, viable and functional after 5 cell divisions with the same level as functionality as prior to cell division + Growth rate is not significantly lower than in equivalent organisms without the synthetic unit
TA4 Species Transferability	+ Unit functions in three major crop species including one monocot and one dicot
TA5 Trait Complexity	+ Unit delivers a complex trait that could not readily be introduced by breeding or gene editing
Overall	+ Synthetic unit functions and is maintained in three major crop species, delivering a complex trait that could not readily be introduced otherwise

SECTION 4: What are we looking for/what are we not looking for

We are interested in:

- Industry partnerships and engagement
- Novel methods for innovating transformation
- Diversity within teams

Research that is out of scope for this programme:

- Research that fits within the broader Programmable Plants Opportunity Space but not within this programme. Rather than submitting to this programme, creators may consider applying for opportunity seed funding, which will be accepting applications in early 2025
- Top-down synthetic chromosomes which are made by altering existing chromosomes rather than being synthesised *de novo*

- Non-nuclear chromosomes
- Episomes
- Synthetic organelles that are not chloroplasts, such as synthetic mitochondria or new-to-nature organelles

SECTION 5: Programme Duration and Project Management

The maximum term of the programme is five years (over both Phases One and Two), though applicants are encouraged to consider plans which may reach success (or failure) on faster timelines. Teams selected at the full proposal stage will enter into a contracting phase with ARIA where the specific scope of work will be finalised. This phase will require updated and more accurate cost assessments for the proposed project.

Project Milestones

Each project's progress will be monitored using clearly defined milestones. Milestones will be defined by the applicant prior to the start of a project, be agreed upon by ARIA, and should be designed to easily convey progress to a third party. In order to do this, milestones should:

+ Be specific, measurable, and signify a meaningful step towards reaching the overall programme goals.
+ Include details on methods used for measurement and evaluation.
+ Be defined on a quarterly cadence for all phases of the programme.
+ Include major "Go / No-Go" decision points.

Success/pivot/closure criteria for each project will be determined by the applicant's ability to meet these agreed-upon milestones.

Programme & project management

During each quarterly project check-in, project teams and the ARIA programme team will review the agreed upon milestones, and discuss further details of each project. As part of that discussion, teams will be encouraged to think through a set of questions as they execute on their plan. These may include the following, provided as an illustrative example:

+ What is(are) the target deliverable(s) for each phase of the programme?
+ What are the top three risks identified at this stage of the project?
+ What are the first three experiments required to overcome each risk?

- What are the expected outcomes/learnings from these experiments?
- How long will these experiments take and how much will they cost?
- What are the dependencies from prior activities/phases of the Programme?

Upon completion of each experiment, questions we will look to answer are:

- What new information has been gleaned?
- What (if any) risks have been overcome? What new risks have emerged?
- Did we learn what we thought we would learn? If not, why not?
- Is there anything we can do to learn more or faster?
- Is there still a path towards the target? Are we heading towards any dead ends?

If you have any additional programme-specific questions, please refer to the published clarification questions here prior to emailing clarifications@aria.org.uk with your query.

If you have any questions on how ARIA funds, please refer to the FAQs here.

Community events

In an effort to foster a collaborative research environment, ARIA will host regular community events to allow the Synthetic Plants programme teams to exchange updates, ideas, and feedback on best paths forward. Creators for all technical areas will be invited to a bi-annual creator event lasting one or two days. Additionally, creators in TA2 will be invited to quarterly workshops between these bi-annual events. All these events will be held in the UK and creators are strongly encouraged to attend. Please include an estimation of costs related to attendance at these events in your budget proposals.

ARIA also plans to host annual in-person workshops where teams can showcase their work to a wider research community, and you may also be invited to additional ARIA networking events. These events will be held in the UK and are optional for creators to attend. If attending these events is of interest to you, please include estimated costs related to attendance at these events in your budget proposals.

SECTION 6: Eligibility & Application process

Eligibility

We welcome applications from across the R&D ecosystem, including individuals, universities, research institutions, small, medium and large companies, charities and public

sector research organisations.

Our primary focus is on funding those who are based in the UK. For the vast majority of applicants, we therefore require the majority of the project work to be conducted in the UK (i.e. >50% of project costs and personnel time).

However, we can award funding to applicants whose projects will primarily take place outside of the UK, if we believe it can boost the net impact of a programme.

In these instances, you must outline any proposed plans or commitments in the UK that will contribute to the programme within the project's duration (note the maximum project duration is 5 years). If you are selected for an award subject to negotiation, these plans will form part of those negotiations and any resultant contract/grant.

More information on the evaluation criteria we will use to assess benefit to the UK can be found later in the document here.

Regulatory considerations for TA1 applications

It is important that applicants proposing to undertake genetic modification activities as part of their proposal are aware of the legislation, regulation, and guidance applicable to such work. This includes, without limitation, the Genetically Modified Organisms (Contained Use) Regulations 2014 (the "Regulations"), the Health and Safety Executive guidance on the Regulations, and the SACGM Compendium of Guidance. Applicants are required to flag any significant legal or regulatory dependencies in their proposals (such as prerequisite licences, permissions, or registrations) and any associated timeline implications. It is a requirement of ARIA funding that all activities are undertaken in compliance with applicable laws.

This will also apply to creators working on TA3, TA4 and TA5 as part of Phase Two of the programme.

Collaboration and Intellectual Property

To facilitate data sharing, some relevant data will be requested in standardised formats for the programme. We expect all results to be reproducible.

This programme will use ARIA's standard approach to Intellectual Property (IP): creators will own any new IP generated as a result of the grant/contract. We endeavour to enable all creator teams to feel that they are a part of a greater whole: the entire programme team of all creators. We encourage collaborative sharing of information (such as research data and findings) between creator teams throughout the programme, facilitated by our regular in-person creator events. We specifically encourage sharing of IP between creator teams at the end of Phase One in order to facilitate progress in Phase Two. If new creator teams assemble at the end of Phase One, sharing of IP between the original teams will be essential.

Finding potential collaborators and teaming

We welcome applications from individuals or teams with expertise in one or more TAs. We strongly encourage collaboration between different sectors (e.g. academia, industry) within creator teams.

For those seeking specific expertise to support their proposal, we have created a teaming request form to facilitate finding potential team members who have registered their interest in this programme. By following the link to the sign up form here you will be able to register, submit your details, and gain access to a list of other individuals seeking to find/share their expertise. All requests are screened via ARIA's internal team prior to access, after which connections will be made by individual users based on their consent and aligned expertise.

ARIA will also host an in-person event on the afternoon of 11 September 2024 for creators who are interested in teaming to be able to meet each other in-person. Details of this event will be shared with those who select they are interested in attending the event as part of the above form to express interest in teaming.

Application Process

Creators are welcome to apply to work on TA1 and TA2 during Phase One, but should they be selected and funded to work on TA1, they will not be selected to work on TA2 and *vice versa*.

The application process for Technical Areas 1 - 5 consists of two stages:

Application Stage 1 - Concept paper

Concept Papers are designed to make the solicitation process as efficient as possible for applicants. By soliciting short concept papers (no more than three pages) ARIA reviewers are able to gauge the feasibility and relevance of the proposed project and give an initial indication of whether we think a full proposal would be competitive. Based on this feedback you can then decide whether you want to submit a full proposal. You can find out more about ARIAs review process here.

If you miss the deadline for submission of concept papers you may still submit a full proposal. However, we strongly encourage you to submit a concept paper. On average, only 8% of applicants that do not submit a concept paper are selected for award.

To ensure the process is quick and open we do not require your organisation's consent prior to submission of a concept paper.

You can find guidance on what to include in a concept paper here.

Following review of concept papers, applicants will either be encouraged or discouraged from submitting a full proposal. For more details on the evaluation criteria we'll use, click here.

Application Stage 2 - Full proposals

This step requires you to submit a detailed proposal including:

- **Project & Technical information** to help us gain a detailed understanding of your proposal
- **Information about the team** to help us learn more about who will be doing the research, their expertise, and why you/the team are motivated to solve the problem
- **Administrative questions** to help ensure we are responsibly funding R&D. Questions relate to budgets, IP, potential COIs etc

You can find more detailed guidance on what to include in a full proposal here. **You can submit a full proposal even if you did not submit a concept paper.**

For more details on the evaluation criteria we'll use, click here.

SECTION 7: Timelines

This call for project funding will be open for applications as follows (we may update timelines based on the volume of responses we receive):

Applications open	**04 September 2024**
Teaming event	**11 September 2024**
Concept paper submission deadline	**25 September 2024 (12:00 BST)**
Concept paper review & notification of encouraged/not encouraged to submit full proposal sent	**26 September 2024 - 15 October 2024**

At this stage and based on your concept paper, you will either be encouraged/ discouraged to submit a full proposal. If you receive feedback indicating that you are not encouraged to submit a full proposal you can still choose to submit a full proposal. You should note that this preliminary assessment/encouragement provides no guarantee of any full proposal being selected for award of funding.

Full proposal submission deadline	**12 November 2024 (12:00 GMT)**
Full proposal review	**13 November 2024 - 27 January 2025**

As part of our review we may invite applicants to meet with the Programme Director during the period of 06 January - 17 January to discuss any critical questions/concerns prior to final selection — this discussion can happen virtually or we may seek clarification on certain aspects of your proposal via email.

Successful/Unsuccessful applicants notified	**29 January 2025**

At this stage you will be notified if you have or have not been selected for an award subject to due diligence and negotiation. If you have been selected for an award (subject to negotiations) we expect a 1 hour initial call to take place between ARIAs PD and your lead researcher within 10 working days of being notified.

We expect contract/grant signature to be no later than 8 weeks from successful/ unsuccessful notifications. During this period the following activity will take place:

- Due diligence will be carried out
- The PD and the applicant will discuss, negotiate and agree the project activities, milestones and budget details
- Agreement to the set Terms and Conditions of the Grant/Contract. You can find a copy of our funding agreements here

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SECTION 8: Evaluation Criteria

Concept Paper and Proposal Evaluation Principles

To build a programme at ARIA, each Programme Director directs the review, selection, and funding of a portfolio of projects, whose collective aim is to unlock breakthroughs that impact society. As such, we empower Programme Directors to make robust selection decisions in service of their programme's objectives ensuring they justify their selection recommendations internally for consistency of process and fairness prior to final selection.

We take a criteria-led approach to evaluation, as such all proposals are evaluated against the criteria outlined below. We expect proposals to spike against our criteria and have different strengths and weaknesses. Expert technical reviewers (both internal and external to ARIA) evaluate proposals to provide independent views, stimulate discussion and inform decision-making. Final selection will be based on an assessment of the programme portfolio as a whole, its alignment with the overall programme goals and objectives and the diversity of applicants across the programme.

Further information on ARIAs proposal review process can be found here.

Proposal evaluation process and criteria

Proposals will pass through an initial screening and compliance review to ensure proposals conform to the format guidance and they are within the scope of the solicitation. At this stage we will also carry out some checks to verify your identity, review any national security risks and check for any conflicts of interest. Prior to review of applications Programme Directors and all other reviewers are required to recuse themselves from decision making related to any party that represents a real or perceived conflict.

Where it is clear that a proposal is not compliant and/or outside the scope, these proposals will be rejected prior to a full review on the basis they are not compliant or non-eligible.

Proposals that pass through the initial screening and compliance review will then proceed to full review by the Programme Director and expert technical reviewers. In conducting a full review of the proposal we'll consider the following criteria:

1) **Worth Shooting For** – The proposed project uniquely contributes to the overall portfolio of approaches needed to advance the programme goals and objectives. It has the potential to be transformative and/or address critical challenges within and/or meaningfully contribute to the programme thesis, metrics or measures.

2) **Differentiated** – The proposed approach is innovative and differentiated from commercial or emerging technologies being funded or developed elsewhere.

3) **Well defined** – The proposed project clearly identifies what R&D will be done to advance the programme thesis, metrics or measures, is feasible and supported by data and/or strong scientific rationale. The composition and planned coordination and management of the team is clearly defined and reasonable. Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed stage-gates and deliverables clearly defined. The costs and timelines proposed are reasonable/realistic.

4) **Responsible** – The proposal identifies major ethical, legal or regulatory risks and that planned mitigation efforts are clearly defined and feasible.

5) **Intrinsic motivation** – The individual or team proposed demonstrates deep problem knowledge, have advanced skills in the proposed area and shows intrinsic motivation to work on the project. The proposal brings together disciplines from diverse backgrounds.

6) **Benefit to the UK**
There is a clear case for how the project will benefit the UK. Strong cases for benefit to the UK include proposals that:

1. are led by an applicant within the UK who will perform the majority (>50% of project costs spent in the UK) of the project within the UK
2. are led by an applicant outside the UK who seeks to establish operations inside the UK, perform a majority (>50% of project costs spent in the UK) of the project inside the UK and present a credible plan for achieving this within the programme duration.

For all other applicants we will evaluate the proposal based on its potential to boost the net impact of the programme in the UK. This could include:

3. A commitment to providing a direct benefit to the UK economy, scientific innovation, invention, or quality of life, commensurate with the value of the award;
4. The project's inclusion in the programme significantly boosts the probability of success and/or increases the net benefit of specific UK-based programme elements, for example, the project represents a small but essential component of the programme for which there is no reasonable, comparably capable UK alternative.

When considering the benefit to the UK, the proposal will be considered on a portfolio basis and with regard to the next best alternative proposal from a UK organisation/individual.

SECTION 9: How to apply

Before submitting an application we strongly encourage you to read this call in full, as well as the general ARIA funding FAQs.

If you have any questions relating to the call, please submit your question to clarifications@aria.org.uk. Please note that the Programme Director is unable to address queries directly and all queries should be directed to clarifications@aria.org.uk.

Clarification questions should be submitted no later than 4 days prior to the relevant deadline date. Clarification questions received after this date will not be reviewed. Any questions or responses containing information relevant to all applicants will be provided to everyone that has started a submission within the application portal. We'll also periodically publish questions and answers on our website, to keep up to date click here.

Please read the portal instructions below and create your account before the application deadline. In case of any technical issues with the portal please contact clarifications@aria.org.uk.

Application Portal instructions

APPLY HERE