CARB-X
Non-traditional Approaches Long Form Instruction Guide

October 2019

Things to Note:

Applications will be managed through the CARB-X Digital Resources (CDR) web-portal in the system entitled "Online Secure CARB-X Application and Review System" (OSCAR).

The online application has many fields for direct online input. However, the majority of the information supporting the application should be completed on the downloadable fillable templates and subsequently uploaded as a PDF on the "Project details" tab and as an Excel spreadsheet on the "Budget workbook and supportive document" tab. If you do not have access to CDR, please contact carbxapp@bu.edu.

Applications will be handled in a confidential manner in accordance with the CARB-X Non-Disclosure Agreement.

1. CARB-X will ONLY accept applications that have used our application form and budget workbook.
2. CARB-X adheres to certain confidentiality labeling conventions to best protect confidential information, and we strongly suggest that you adopt this labeling: "CONFIDENTIAL – CONTAINS TRADE SECRETS AND COMMERCIAL INFORMATION" on confidential documents that are uploaded into the CDR server.
3. The information marked "non-confidential" below will be used internally as a project summary and to evaluate conflicts of interest. Information in these non-confidential sections should be material that you would discuss publicly and that is acceptable for internal and external disclosure. Such non-confidential material of successful applications may ultimately be shared as part of the description of CARB-X pipeline projects.

File Name Format

Please use the following file name format for all files that you upload into CDR:
FundingRound_YearMonthDay_Your Company Name_Last 4 numbers of your carbx id_Item Name; Note: all lowercase, underscores, and zeros must be present.
e.g. "1_YYYYMMDD_companyname_0435_longformapplication"

1. 1_20191101_companyname_0435_longformapplication
2. 1_20191101_companyname_0435_budgetworkbook
3. 1_20191101_companyname_0435_attachmenta
4. 1_20191101_companyname_0435_attachmenta1
5. 1_20191101_companyname_0435_detailedganttchart
6. 1_20191101_companyname_0435_oda (if applicable)

Table of Contents

The table of contents provides information where entry, upload or attachments are required.

Please review carefully as this is to provide information to our reviewers in a clear and standard format.

Application Section	CDR Online Entry	Comments	Non-confidential or Confidential
Company Information	CDR Online Entry (Cover Sheet)		Non-confidential
Principal Investigator Information			
Application Category		See website	
Funding Information		CARB-X funding is expected to begin at or after May 1st, 2020 for this funding round. Do not include any costs prior to this date in your budget.	
Development Stage		See definitions of the stages within CARB-X funding scope. Therapeutics (Right click link and open)	
Non-confidential Project Summary (from EOI application)		Project summary of 2000 characters or less	
Additional Information:			
History of prior application to CARB-X (if any).			
Will CARB-X funding support: 1. Trials in human? If so, who will be the legal sponsor? 2. Use of animals, and will these studies include any of the following: Non-human primates, Dogs, Cats, Equines? Names of individuals that you do not wish to review your application due to perceived conflicts of interest (if any). Please input exact names as already provided to CARB-X from the decision email. (Exact names)			

Table of Contents (continued)

Application Section	File Upload on CDR	Comments	Non-confidential or Confidential
Long Form Fillable Template Tables and Figures to be included: i. Quad Chart ii. Target Product Profile (TPP) and Competitive Differentiation (CARB-X Template) iii. Compound Selection Cascade – If in Hit to Lead or Lead Optimization iv. Project Structuring Approach v. Go/No-Go Project Milestones Table vi. Risk Register Response: i. Point-by-point to Short Form Feedback	Upload as a single **PDF** with elements incorporated within the LF application using the fillable template provided (Project Details section)	The Short and Long Form reviewers are not the same. The Long Form file should be a standalone document, as the reviewers may not have seen the Short Form. The Point-by-point response to Short Form feedback must show the question and complete response to each feedback item (e.g., providing only a reference to a page number in the application is NOT sufficient).	Confidential
Detailed Gantt Chart – At a task dependent level	File Upload as a **PDF** (Project Details)	A Detailed Gantt Chart, showing all activities for each stage, must be uploaded in CDR as a separate PDF file.	
Animal Compliance Information (both need to be completed) Attachment A Attachment A-1	File Upload as a **PDF** (attach a) and **Spreadsheet** (attach a-1) (Budget Workbook) with any Supporting Documents)	Helpful Information Animal Compliance: CARB-X Research Compliance Animal Compliance Webinar	
Budget Workbook and Supportive Documents Template Budget Workbook	File Upload as a **Spreadsheet** (Budget Workbook) with any Supporting Documents	Helpful Information Budget Workbook General Budget Feedback and Inclusions Overview of Federal Grant Compliance Regulations for Profit Overview of Federal Grant Compliance Regulations for Not-for-Profit	
Official Development Assistance (ODA) (if applicable) ODA Justification Form	File Upload as a **PDF** (ODA Justification)	Helpful Information ODA: ODA Eligibility Requirements ODA Considerations	

Guidance for the Long Form Fillable Template

Formatting requirements - Applications that do not meet the following formatting requirements WILL NOT be reviewed. Do not change the formatting of the document.

1. The application must be formatted with a 12-point Times New Roman font. When pasting in tables etc. from other documents, other fonts may be acceptable if text is easily visualized on screen.
2. The total number of Long Form pages cannot exceed **45**. Section A: suggested 35 pages in total and Section B: suggested 10 pages in total; however, the number of pages within each section is only indicative.
3. The Table of Content page is **excluded** from the 45-page limit. A total of 46 pages when saving as a PDF (includes the Table of Content and Appendix) is allowed.
4. The application should be **DATA RICH**, including Figures and Tables where appropriate to support the status of the program. A word description of data is **not** adequate. Indicate which data is for which molecule. Ensure the legends and the labeling of the figures and tables are clear to readily understand how the data were generated and the sources for the data points.
5. Confirm the footer continues to read "CONFIDENTIAL – CONTAINS TRADE SECRETS AND COMMERCIAL INFORMATION" on all pages. Confirm page numbers are inserted.
6. Do not remove hyperlinks.
7. No hyperlinks in the text leading to external websites.
8. No embedded files are permitted within the PDF.

Applications will be screened for content requirements prior to distribution to reviewers. Applications that do not meet the **content requirements** WILL NOT progress into the review process.

Do **not** include references. Do include data from your other programs if it helps to explain and/or validate your technology/approach.

Long Form Fillable Template

The guidance text in the fillable template should be overwritten.

(Right click link and open)

Section A: Project Details

The following items **must** be included **within** the Long Form Fillable Template:

i. Quad Chart
ii. Target Product Profile (TPP) and Differentiation Matrix (CARB-X Template)
iii. Compound Selection Cascade – If in Hit to Lead or Lead Optimization
iv. Project Structuring Approach
v. Go/No-Go Project Milestones Table
vi. Risk Register

Quad Chart

Vision for the Project: One sentence statement Objective: Clear, concise, 2-3 sentence description of the objectives and methodologies of the project Target Product Profile Summary: Provide the following Indication(s) and patient population(s) Pathogen(s) covered Route of administration and dose regimen Description of Effort: A bullet list (2-3 entries) of the scientific challenges to be addressed using the proposed CARB-X funding	Picture or Graphic illustrating the project or concept (e.g., data figures, molecule illustrations, or processes)
Benefits of Proposed Project: Challenges: Current Phase of Technology (choose from list below): • Hit-to-Lead • Lead Optimization • Pre-Clinical • Phase 1 Identify whether it is for Treatment or Prevention (choose from list below): • Treatment • Prevention	**Base Stage: total $XXX / CARB-X $YYY. Company cost share Z%. Duration # of months** Bullet list of major goals/milestones by Major Milestones **Option Stage 1: total $XXX / CARB-X $YYY. Company cost share Z%. Duration # of months** Bullet list of major goals/milestones by Major Milestones **Option Stage 2: total $XXX / CARB-X $YYY. Company cost share Z%. Duration # of months** Bullet list of major goals/milestones by Major Milestones **Option Stage 3: total $XXX / CARB-X $YYY. Company cost share Z%. Duration # of months** Bullet list of major goals/milestones by Major Milestones

Target Product Profile and Competitive Differentiation Matrix

CARB-X Therapeutics – Target Product Profile		
Variable	Minimal Requirement	Ideal Requirement
Primary Product Indication		
Organisms covered		
Patient Population		
Treatment Duration		
Delivery Mode		
Dosage Form		
Regimen		
Efficacy		
Risk/Side Effect(s)		
Competitive Differentiation Envisioned for Product Launch (consider marketed products + those in developments)	Minimal Requirement	Ideal Requirement
Specific Populations Claims		
Key Differentiating Claims		
Overall Value Proposition: Summarize what the desired product would bring to the infectious disease physicians armamentarium:		

Target Product Profile (TPP) (CARB-X Template)

(Right click link and open)

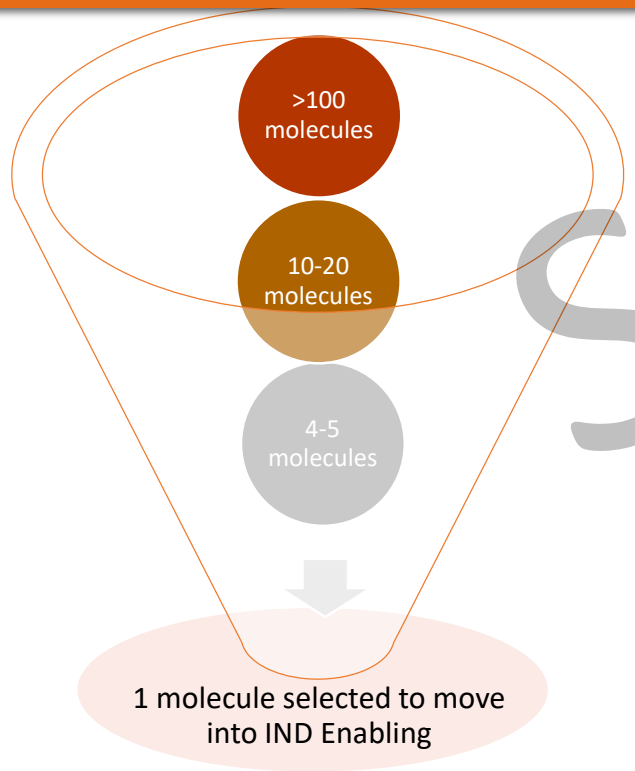
Competitive Differentiation Matrix			
	Competitor 1	Competitor 2	Competitor 3
Overview: Brief description of how the competitor is used clinically, whether it is considered standard-of-care. Are there dosing restrictions in certain populations etc.?			
Differentiation Areas: What liabilities do the competitor molecules possess and which attributes will your product have/need to enable penetration into the marketplace? Add rows for each general category (e.g. safety, dosing regimen etc.)			
Clinical Comparator: Will this compound likely be a comparator used during clinical development of your product?			

The competitor products should also include those that are currently in clinical development and may represent the standard-of-care in the future.

Example

Compound Selection Cascade (If in HTL to LO)

Drug development: starting with the final product profile in mind enables the right foundation to be laid at the start



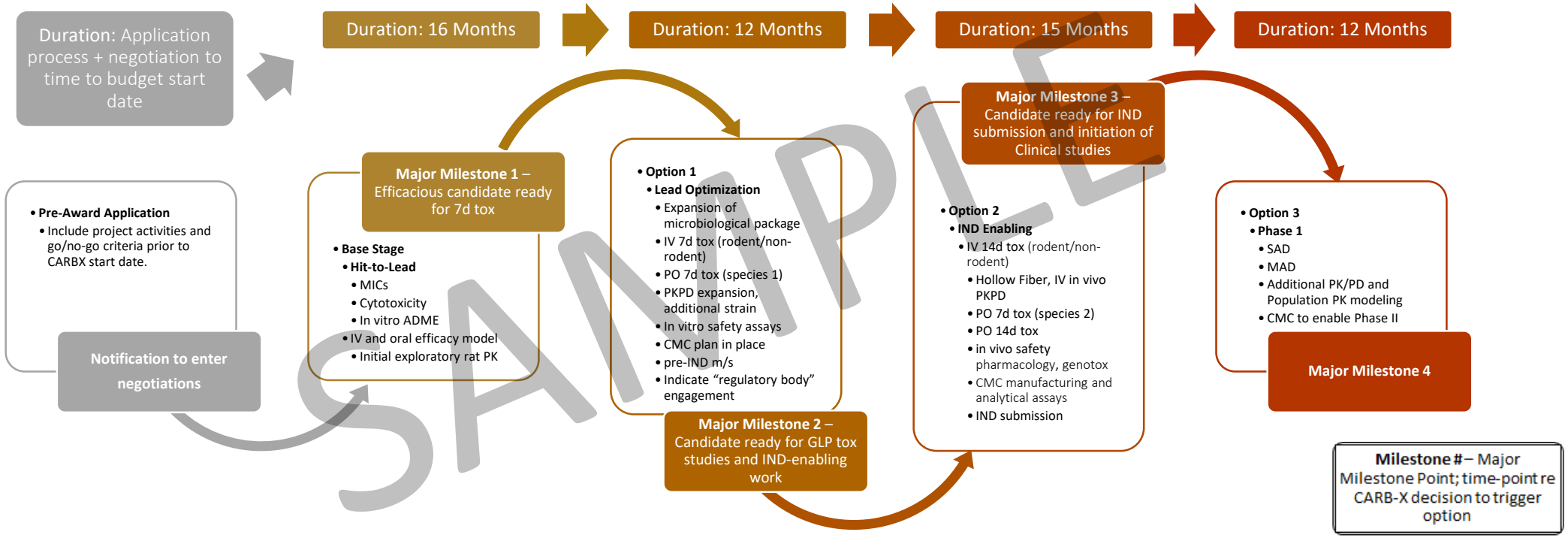
Molecule(s)	Examples of Studies	Attributes for the molecule to move forward. What are the quantitative desired candidate profile criteria?
>100	• in vitro MICs • Cytotoxicity • Solubility	• Microbiological potency • Measure of movement across membranes • Cytotoxicity: reduced likelihood of eukaryotic toxicity in vivo • Solubility sufficient for in vitro and in vivo studies
10-20	• ADMET • In vivo PK • Population MICs and secondary panel • Frequency of resistance (FoR)	• Suitable availability of drug (low plasma protein binding, high metabolic stability, etc.) • Good pharmacokinetics • Appropriate microbiological spectrum and impact of pre-existing resistance mechanisms • Low propensity for resistance emergence
10	• in vivo efficacy lung/thigh • In vitro safety and secondary pharmacology assays • Metabolite ID	• In vivo efficacy: Single and repeat dose to confirm in vivo pharmacologic effects • Reduced risk of off-target toxicological effects • Support choice of toxicological test species
4-5	• PK/PD • Formulation assessment • Pilot toxicity /TK (rat, dog) • API and drug product assessment • in vivo genotoxicity • Expanded microbiological assays	• PK/PD driver identified to support choice of dosing regimen • Identification of suitable formulation to support higher doses used in toxicological studies • Determination of MTD and impact of repeat dosing (e.g. accumulation) to support design of pivotal toxicology studies • Ease of API production and impact of cost of goods • Reduced risk of genotoxicity • Level of bacterial killing, presence of post-antibiotic effect, etc.
1	Molecule selected	

CARB-X
Combating Antibiotic Resistant Bacteria

BOSTON UNIVERSITY

Example (For a project in Hit-to-Lead during the Base Stage)

Project Structuring Approach



This should include work that is planned to be carried out 1) between the application date and potential budget start date if awarded and, 2) work to be carried out during the timeline of the CARB-X supported project that might be funded outside of the CARB-X agreement.

The above example of project structuring is **indicative only**. Listed activities need to be specific to the work described in the application. In many cases, the stages follow normal drug development phases (i.e., BASE Stage = Hit to Lead, Option 1 = Lead Optimization, etc.), but it is not a strict requirement. The proposed structure should be what makes most sense for the specific needs of the project. Projects are not required to start from Hit-to-Lead nor to run through Phase 1.

CARB-X's scope of funding extends to completion of a Phase 1 SAD/MAD. If applicant is interested in CARB-X support out to and including a clinical trial, this should be included now in your Short Form application (including appropriate details in Project Structure Approach, Milestones, Risk Register, Clinical expertise, Budget Workbook, etc.). If not included, applicant will need to submit a separate application in a future funding round to apply for Ph1 testing.

Go/No-Go Project Milestones

- The CARB-X Advisory Board needs to understand the full plan of activities and associated milestone Go/No-go criteria, and risk mitigation strategies, including those activities CARB-X is not being asked to fund. It is essential that CARB-X and its Ad Board members understand the holistic plan and the appropriate risk mitigation of it.
- Define the Major Milestone deliverable at the end of each stage (e.g., short list of xx scaffolds to further optimize in "LO" or "Preclinical Candidate nominated").
- Identify measurable "Go Criteria" and "No-go Criteria" for each Go/No-go Project Milestone, including required reports to demonstrate completion of each Go/No-go Project Milestone within the proposed stage. Go/No-go criteria must be specific, objective, and quantitative.
- Include milestones for any other work (funded by other sources) that will be conducted concurrently during the CARB-X funding period, clearly marking these milestones as funded by other sources.
- Definitive and rigorous milestones will be viewed positively as communicating your organization's understanding of the importance of making early and data-driven decisions.
- The following slide provides a framework for project milestones that can be used as a reference.

Exemplar Go/No-Go Milestones

Hit to Lead

- MIC90 target against specific pathogen ≤ X µg/ml
- Cytotoxicity > X µg/ml or µM
- Frequency of resistance not > than Y at X-fold MIC
- In vivo efficacy demonstrated in relevant infection model
- Quantitative *in vitro* ADME criteria (e.g. microsomal clearance, protein binding, solubility etc.)
- CMC

Lead Optimization

- MIC90 target against specific pathogen/TPP pathogens ≤ X µg/ml
- Frequency of resistance ≤ Y at X-fold MIC
- Mechanism of resistance understood
- Bioavailability > X% and/or PK profile consistent with intended dose regimen
- Efficacy demonstrated with multiple TPP pathogen(s) isolates
- PK/PD driver and magnitude range established and median value leads to achievable predicted human dose
- Quantitative *in vitro* safety criteria (e.g. hERG, secondary pharmacology panel etc.)
- MTD established in toxicological species
- NOAEL in multi-day non-GLP toxicology study > X mg/kg with evidence of safety margin > X-fold
- API: sufficient quantity with quality suitable for GLP toxicity studies
- Regulatory path: pre-IND consultation completed

IND enabling

- Population microbiology on large (>100 isolates of each TPP species) panels of recent clinical isolates confirms MIC90 values
- GLP tox studies: toxicology issues identified that would prevent dosing in humans. NOEL or NOAEL clearly defined (numeric)
- Acceptable safety margin (>X fold) in *in vivo* genotoxicity and safety pharmacology (cardiovascular, CNS, respiratory)
- CMC: clinical manufacturing route established and full characterization on clinical material complete
- IND documentation submitted/cleared

Phase I

- Appropriate documentation at clinical study site approved
- Favorable benefit/risk for tolerability, safety, and pharmacokinetics of single and multiple ascending doses studies
- Human PK incorporated into PKPD model and tolerable Phase II doses predicted to be efficacious
- API: clinical supply chain established

These are indicative only and the expectation is that the project milestones are quantitative in nature based on the individual project specifics.

GO/NO-GO Project Milestones					
Milestone#	GO/NO GO Contract Milestones	Go Criteria	No-Go Criteria	SOW/Technical Report	Stage of Plan (Base, Option 1, etc.)
1					
2					
3					

CARB-X
Combating Antibiotic Resistant Bacteria

BOSTON UNIVERSITY

Risk Register

Please identify potential risks for your program, explaining the probability of occurrence and impact (level and nature) of the risk. Describe the mitigation strategy for each potential risk. Identifying the probability or impact of all risks as “low” would be viewed critically.

Risk Register				
Risk	Probability of Occurrence (High, Medium, Low)	Impact to Project (High, Medium, Low)	Nature of Impact (Cost, schedule, product profile etc.)	Mitigation Strategy

Detailed Gantt Chart – at a task dependent level

- A Detailed Gantt chart is to communicate information to project stakeholders. In this chart, you must communicate task dependencies: This makes it very clear which tasks are dependent on one another, and easy to assess the impact of different scenarios on the project.
  - The task list
  - Task start and end dates
  - Task durations
  - The project start and completion dates
  - Project milestone dates
  - The project completion date
- Indicate project elements that would be funded by CARB-X or other funding agencies.
- Indicate what activities are occurring and what data are expected between Long Form submission and the projected start of CARB-X Funded program.
- While CARB-X will not fund projects beyond Phase 1, include a high-level development plan downstream of Phase 1. This is helpful to demonstrate that challenges and requirements of later-stage clinical development and regulatory filings are appreciated and that related activities are incorporated early enough into the plan to avoid delays in starting later stage trials.

Point-by-point response to Short Form feedback

- ❑ The Point-by-point response to Short Form feedback must be included in the Long Form Fillable Template.
  - ❑ The Point-by-point response to Short Form feedback must show the question and answers to each feedback item. The Short Form feedback answers need to be complete and not just reference the Long Form page number. (with the exception of figures/tables)
  - ❑ The Short and Long Form reviewers are not necessarily the same. Please include full background description, scientific rationale and supporting data in body of Long Form.
  - ❑ The Long Form document must be completely standalone. Do not reference back to the Short Form or to the Point-by-Point responses to Short Form Feedback.

Detailed Budget Summary

A separate Excel workbook is provided to enter detailed budget information. Please take note of the following important points when assembling your budget:

Template Budget Workbook | General Budgeting Feedback and Inclusions | Sample CARB-X Research Subaward Agreement

(Right click links and open)

- ❑ A minimum cost share of 10% per stage is required from Hit-to-Lead through Preclinical. Phase 1 must meet minimum cost share of 20%.
- ❑ U.S. federal or state/local governments funds (including NIH and SBIR grants) cannot be used towards cost share.
- ❑ UK government grants (e.g. Innovate UK and other UK sources) may count toward cost share, up to a specified limit. Contact CARB-X to discuss.
- ❑ Other non-US federal/state government grants may count toward cost share if written documentation of the sponsoring agency's approval is provided. Contact CARB-X to discuss.
- ❑ All expenses charged to cost share need to meet US federal compliance guidelines (e.g. animal and human subject compliance).
- ❑ Reimbursement for animal studies is only allowable after the animal compliance requirements are met.

For US-based companies, a 10% *de minimis* rate is applicable unless your organization has an existing Rate Agreement with the federal government. Any existing Rate Agreement must be submitted with the Long Form Budget Workbook in CDR.

CARB-X cannot sponsor any new requests for a federally negotiated rate agreement

CARB-X cannot fund any costs related to work carried out prior to the start of the period of performance. CARB-X funding is expected to begin at or after May 1st, 2020 for this funding round. Do not include any costs prior to this date in your budget.

Pre-award costs are strictly unallowable and cannot be reimbursed. However, in anticipation of a project start date;

1. Supply orders may be submitted before the study start date as long as
   - ❑ payment is submitted after the start date and
   - ❑ materials are received after the start date
2. Certain pre-study costs for animal studies are allowable after the project start date including:
   - ❑ startup costs incurred for the purpose of holding a slot with the CRO
   - ❑ preparation of documentation for study protocols, IACUC approval, VAS
   - ❑ personnel time for study planning and protocol review

General Information

- Applicants who do not already have a DUNS number and are not already registered in the System for Award Management (SAM) should begin this process now to be able to move efficiently along the application process. Ultimately, successful applicants will be required to have a DUNS number and SAM registration.

- To obtain a DUNS number, access the Dun and Bradstreet website at http://www.dnb.com/duns-number.html, or call 1-866-705-5711.

- For SAM registration, access the SAM website at http://www.sam.gov, or by phone at 1-877-252-2700. User Guides and FAQ are available on the "Help" tab of the SAM website.

Sample Scoring Tool

Scoring Tool that the Ad Board members will use to score your application.

Sample Scoring Tool

(Right click link and open)

Animal Compliance – Attachment A, A-1 & Vertebrate Animal Section (VAS)

Attachment A, Attachment A-1 and the Vertebrate Animal Section (VAS)* must be uploaded to the CDR system at the same time as the Long Form. Please refer to the links below for an overview of the compliance requirements for animal studies as these may impact your assumptions on plan timing and costs. We cannot reimburse for animal studies initiated without addressing the animal compliance requirements.

Please upload these documents in the same upload area as your Long Form Project Details Application.

**You may use the VAS template provided or your own. If you use your own, please ensure it includes all four sections required by OLAW*

Attachment A	Attachment A-1	Vertebrate Animal Section (VAS)	Please review our website for information relating to Research Compliance

(Right click links and open)

Official Development Assistance (ODA) Justification Form (if applicable)

Part of CARB-X's funding is available through our partnership with the UK's Global AMR Innovation Fund (GAMRIF) to support the economic development and welfare of developing countries through the ODA program. To be considered for this funding, applicants must complete the *ODA Justification Form*

- For a description of what is eligible for ODA funding, please refer to the *ODA Eligibility Requirements* document
- To help articulate your justification, please refer to the *ODA Considerations* document.

Please upload your *ODA Justification Form* into the specific upload area in CDR. This must be submitted with the Long Form documents.

ODA Eligibility Requirements | ODA Justification Form | ODA Considerations | ODA Recorded Webinar | ODA Webinar Slides

(Right click links and open)

NIAID Preclinical Services

In the Long Form, explain areas or challenges to your program where NIAID's partnership could contribute to the success of your program.

Please refer to the following website providing of a NIAID's standard preclinical services: https://www.niaid.nih.gov/research/pre-clinical-models-infectious-disease. NIAID is one of CARB-X's strategic partners and provides funding to CARB-X in the form of in-kind support. **It is a requirement** that applicants consider what critical gaps NIAID services might fill in their programs.

Please refer to the NIAID Preclinical Services slide deck below for a description of available support. Successful applicants in the CARB-X process will have streamlined access to NIAID's development resources.

NIAID PCS Slide Deck

(Right click link and open)

Questions?

During the application process, your primary point of contact will be CARB-X (carbxapp@bu.edu).