CARB-X
Non-traditional Approaches
Short Form Instruction Guide

July 2019

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CARB-X
Combating Antibiotic Resistant Bacteria

BOSTON UNIVERSITY

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 your other documents that is 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. In addition, such non-confidential material of successful applications may ultimately be shared as part of the description of CARB-X pipeline projects.

Please use the following filename format for all files that you upload into CDR: round_month_year_company name_the last 4 numbers of your carbx id_item name; e.g. "1_july_2019_carbx_0435_shortformapplication", **all lowercase, underscores, and zeros must be present.

1. 1_july_2019_carbx_0435_shortformpplication
2. 1_july_2019_carbx_0435_budgetworkbook
3. 1_july_2019_carbx_0435_oda (if applicable)

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Table of Content

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, if required	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? 3. List of reviewers that applicant does not wish to evaluate application. Name individuals which 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.			

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Table of Content (continued)

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	File Upload on CDR	Comments, if required	Non-confidential or Confidential
Short 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	Upload as a single **PDF** with elements incorporated within the SF application using the fillable template provided (Project Details section)		Confidential
Budget Workbook and Supportive Documents Template Budget Workbook	File Upload as a **Spreadsheet** (Budget Workbook) with any Supporting Documents	Helpful Information Budget Workbook and Supportive Documents: 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	

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Guidance for the Short 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 in 12-point simple font and easily visualized on screen.
2. The total number of Short Form pages cannot exceed **15**. Section A: suggested 12 pages in total and Section B: suggested 3 pages in total; however, the number of pages within each section is only indicative.
3. 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.
4. Confirm the footer continues to reads "CONFIDENTIAL – CONTAINS TRADE SECRETS AND COMMERCIAL INFORMATION" on all pages. Confirm page numbers are inserted.

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 or citations of foundational information on AMR. Do include data from your other programs if it helps to explain and/or validate your technology/approach.

Short Form Fillable Template

The guidance text in the fillable template should be overwritten.

(Right click link and open)

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Section A: Project Details

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

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

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Quad Chart

Vision: One sentence statement Objective: Clear, concise, 2-3 sentence description of the objectives and methodologies of the project Target Product Profile: Provide the following Indication(s) and patient population(s) Pathogen(s) 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

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Target Product Profile and Competitive Differentiation Matrix

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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 and Competitive Differentiation Matrix (TPP) (CARB-X Template)

(Right click link and open)

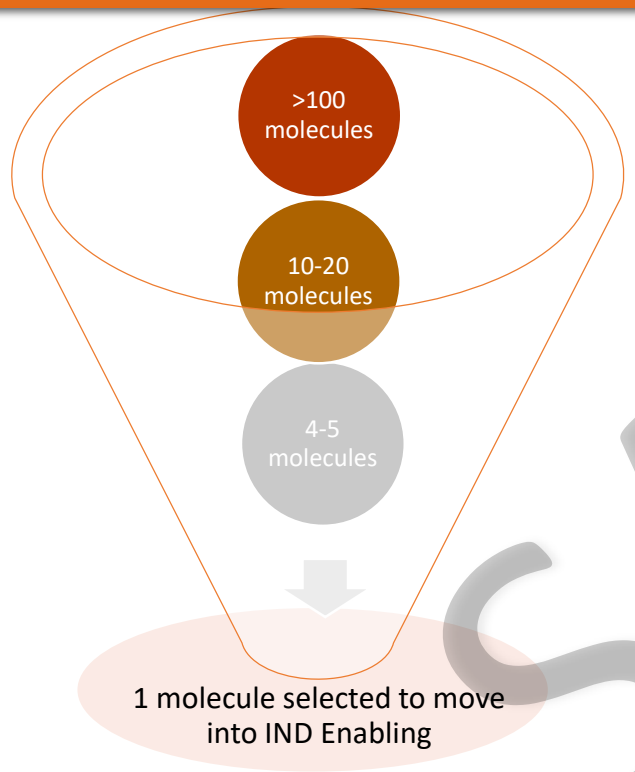
Competitive Differentiation Matrix			
	Competitor 1	Competitor 2	Competitor 3
Overview: Brief description of how the competitor is used clinically, whether it is considered standard-of-care. Are there dosing restrictions in certain populations etc.?			
Differentiation Areas: What liabilities do the competitor 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 • PK/PD • In vitro safety and secondary pharmacology assays • Metabolite ID	• In vivo efficacy: Single and repeat dose to confirm in vivo pharmacologic effects • PK/PD driver identified to support choice of dosing regimen • Reduced risk of off-target toxicological effects • Support choice of toxicological test species
4-5	• Formulation assessment • Pilot toxicity /TK (rat, dog) • API and drug product assessment • in vivo genotoxicity • Expanded microbiological assays	• 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	

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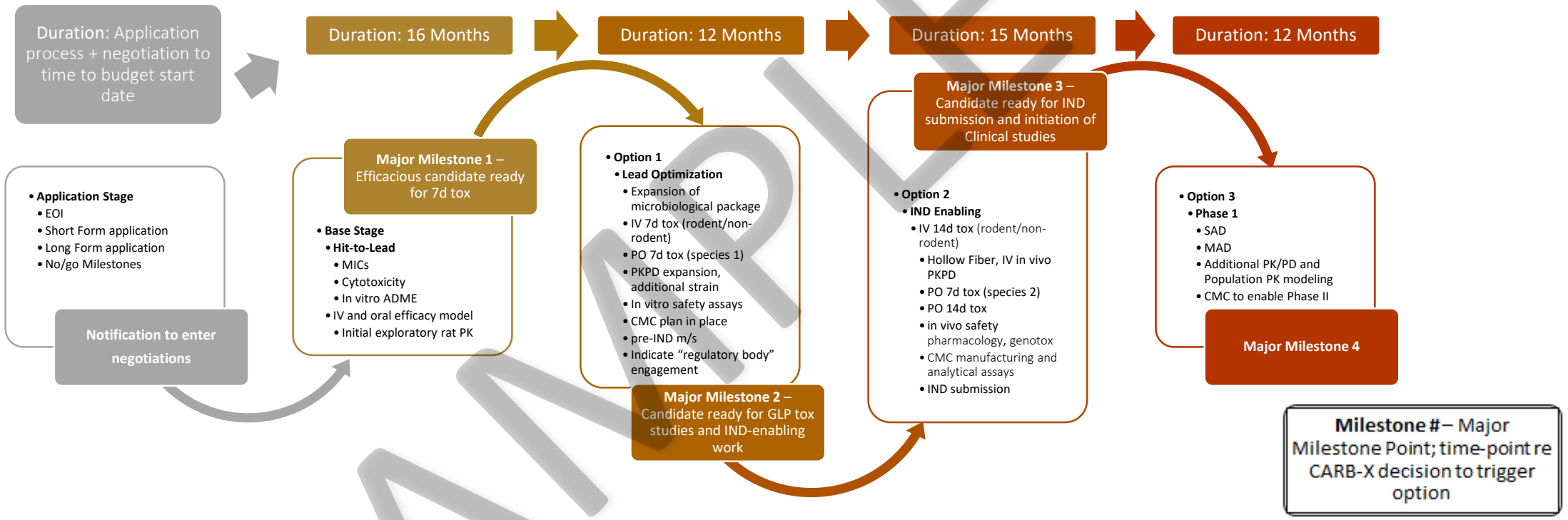
Example (For a project in Hit-to-Lead during the Base Stage)

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**. 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 Phase 1. If applicant is interested in CARB-X support out to and including, Phase 1, this should be included now in your Short Form application (including appropriate details in Project Structure Approach, Milestones, Risk Register, Budget Workbook, etc.). If not included, applicant will need to submit a separate application in a future funding round to apply for Phase 1 testing.

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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 provide a framework for project milestones that can be used as a reference.

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Exemplar Go/No-Go Milestones

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Hit to Lead

- MIC90 target against specific pathogen ≤ X µg/ml
- Cytotoxicity > X µg/ml or µM
- Frequency of resistance not > than XX 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 ≤ X 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					

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

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High Level Budget Summary

A High-Level Budget Workbook is provided. **It is a high-level, preliminary/non-binding budget template to accompany the Short Form (SF) application.** It is not intended to be precise; rather, it serves to give CARB-X an idea of the requested costs and size of project. Applicants moving forward to the Long Form (LF) submission will have an opportunity to submit an updated, detailed budget at that later stage.

Template Budget Workbook | 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* indirect 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 if
   - ❑ payment is submitted after the start date and
   - ❑ materials are received after the start date
2. Certain pre-study costs for animal and human subject research 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 documentation
   - ❑ personnel time for study planning and protocol review

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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.

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Sample Scoring Tool

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

Sample Scoring Tool

(Right click link and open)

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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 Short Form documents.

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

(Right click links and open)