6 July 2018

ODA Considerations for CARB-X Funded Projects

CARB-X[1] is a global non-profit funder of preclinical R&D targeting the most dangerous drug-resistant bacteria designated by the WHO. Starting in 2018, CARB-X now receives funding from the UK Department of Health and Social Care, through their Global AMR Innovation Fund (GAMRIF). GAMRIF funds come from the UK's Official Development Assistance (ODA) budget. CARB-X therefore has additional funds available for projects that qualify as ODA.

ODA is government aid with a primary intention to: (A) promote the welfare and economic development of low- and middle-income countries on the OECD "Development Assistance Committee" list ("Developing Countries"); and (B) benefit directly and primarily people in Developing Countries.[2] We first explore the application of these latter two standards to CARB-X before concluding with an analysis of "primary intention" and "secondary beneficiaries."

The product developer is responsible for describing to CARB-X how their project is ODA eligible. CARB-X will review the descriptions, giving comments where appropriate, and will make decisions regarding ODA funding. ODA-eligibility is based on guidelines from the OECD.[3]

A. Promote the welfare and economic development of Developing Countries

The "Developing Country welfare and economic development" standard is likely met by any CARB-X project because the intention of CARB-X is to reduce the threat to human health from drug-resistant bacterial infections, which is noted by both the United Nations General Assembly[4] and the World Health Assembly[5] to be a global threat to health. The UN General Assembly particularly noted "that antimicrobial resistance challenges the sustainability and effectiveness of the public health response to these and other diseases as well as gains in health and development and the attainment of the 2030 Agenda."[6] Antimicrobial resistance "gravely challenge[s]" many public health achievements brought by social and economic development; hygiene, safe water and sanitation; disease prevention; nutrition and

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[1] CARB-X, www.CARB-X.org.

[2] ODA-eligible research:

- Has to target problems directly and primarily relevant to Developing Countries;
- Should investigate a specific problem or seek a specific outcome which will impact Developing Countries in the immediate or longer-term;
- Demonstrate appropriate pathways to impact that ensure the Developing Countries benefit from the research; and
- While Developing Countries should be the primary beneficiaries, the research can also be relevant and have secondary benefits for other countries.

Dr. Kate Hamer, Head of International, NERC. Official Development Assistance in the Research Context, slide 4 (undated) (available at https://nerc.ukri.org/research/partnerships/international/gcrf/news/workshop-outcomes/gcrf-workshop-kate-hamer/).

[3] OECD (Development Assistance Committee). Converged Statistical Reporting Directives for the Creditor Reporting System (CRS) and the Annual DAC Questionnaire (8 Apr 2016) (available at https://www.oecd.org/dac/financing-sustainable-development/development-finance-standards/DCDDAC(2016)3FINAL.pdf).

[4] Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance A/RES/71/3 (22 Sept. 2016).

[5] Global action plan on antimicrobial resistance WHA68.7 (26 May 2015).

[6] Political Declaration, at par. 2.

healthy food; and other health achievements.[7] All of these efforts will also support progress towards achievement of Sustainable Developent Goal 3, with reductions in communicable diseases and improved access to medicines.[8]

The UN General Assembly specifically called for "sustained research and development" investments like those undertaken by CARB-X, that are aimed at "resolving the lack of investment in research and development, including through the provision of incentives to innovate and improve public health outcomes, particularly in the field of antibiotics[.]"[9] CARB-X supports "basic and applied innovative research and development," supporting "research and development on quality, safe, efficacious and affordable antimicrobial medicines, especially new antibiotics and alternative therapies, vaccines and diagnostics[.]"[10]

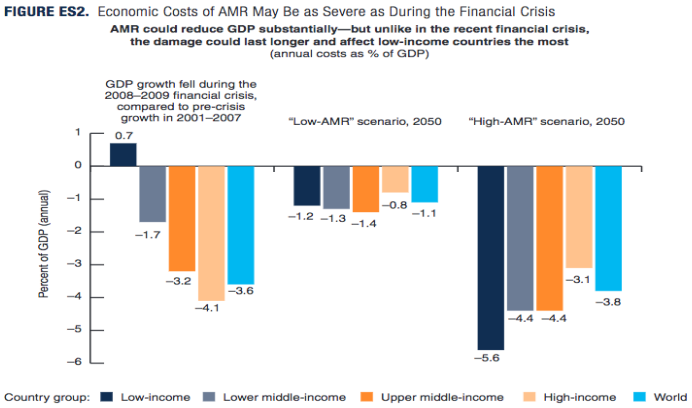
Similarly, the 2015 World Health Assembly highlighted "that hard-won gains in health and development, in particular those brought about through the health-related Millennium Development Goals, are put at risk by increasing resistance to antimicrobials" constituting a threat in high-, middle- and low-income countries.[11] Countries were challenged to create National Action Plans in response; as of May 2018, 58 National Action Plans have been published on the WHO website.[12] Many of these National Action Plans are also linked to the Global Health Security Agenda.[13] For come countries, Joint External Evaluation Mission Reports are available on these issues.[14]

Antimicrobial resistance also threatens economic prosperity. In 2016, the World Bank projected the economic effects of antimicrobial resistance. In the "optimistic" case (scenario), annual gross domestic product would fall by 1.1%; the AMR shortfall would exceed $1 trillion annually by 2030. The "high-impact" case was more than three times worse.[15] In both cases, the disproportionate impact will fall on Developing Countries:

Poorer Countries Will Suffer Most
Moreover, with AMR, low-income countries would experience larger drops in economic growth than wealthy countries, so economic inequality between countries would increase. The differential impacts on GDP result from higher infectious disease prevalence and greater dependence on labor incomes in countries with lower per capita incomes.[16]

A Figure from the World Bank report illustrates the magnitude of the risk and the disproportionate impact on poorer countries:[17]

[7] Political Declaration, at par. 4.
[8] Sustainable Development Goal 3, https://sustainabledevelopment.un.org/sdg3.
[9] Political Declaration, at par. 9.
[10] Political Declaration, at par 10(b).
[11] Global action plan, at chapeau.
[12] WHO, Library of National Action Plans (visited 25 May 2018).
[13] Global Health Security Agenda, https://www.ghsagenda.org/assessments.
[14] Joint External Evaluation Mission Reports, http://www.who.int/ihr/procedures/mission-reports/en/.
[15] World Bank, Drug-resistant infections: a threat to our economic future (Executive Summary, March 2017), at 6.
[16] Id.
[17] Id., at 7.



It should be noted that most of the published reports follow the more inclusive term "antimicrobial resistance" or "AMR," while the scope of CARB-X is more limited to drug-resistant bacterial infections. The WHO undertook an expert review of available evidence of the global burden of drug-resistant bacteria when it produced the Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics.[18] CARB-X uses this list to define scope for fundable projects. When possible, applicants should include any additional information about the burden in Developing Countries of the specific drug-resistant bacteria targeted by the project, from the published literature. Currently, the Global Burden of Disease project is working on estimates for AMR, including drug-resistant bacteria.[19]

Given these data from the relevant UN institutions and the mission of CARB-X, any CARB-X funded project is likely to be able to meet the broad "Developing Country welfare and economic development" standard for ODA-eligibility.

B. Benefit directly and primarily people in Developing Countries

1. Direct benefit

"Direct" benefit for people in Developing Countries is clear: millions of people in Developing Countries are affected by drug-resistant infections, requiring the actions called for by the UN General Assembly, the World Health Assembly, and the relevant National Action Plans. In particular, CARB-X requires, as a contractual condition to receive funding, that each recipient commit to directly benefitting people in Developing Countries through a transparent Stewardship and Access Plan, supported by Wellcome Trust, and backstopped with Access Rights available to Wellcome Trust to promote access to CARB-X funded antimicrobial products, especially in Developing Countries for which the company does not seek a commercial market.

[18] Tacconelli E, et al. Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics, 2017 (available at http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf).

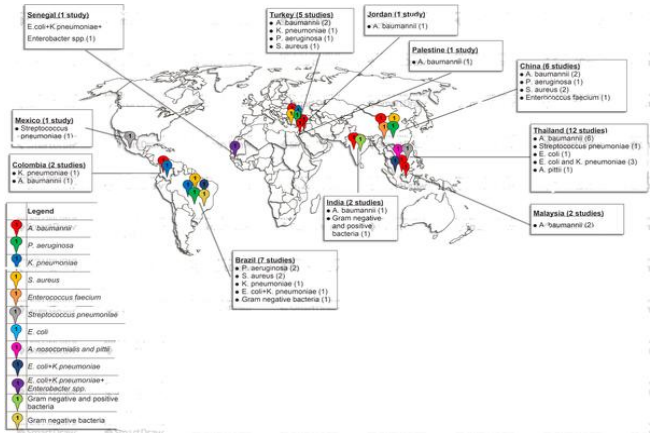
[19] Kaiser Family Foundation. Wellcome Trust, Partners Launch Global Burden Of Disease AMR To Take Action On Antimicrobial Resistance (16 Oct 2017) (available at: https://www.kff.org/news-summary/wellcome-trust-partners-launch-global-burden-of-disease-amr-to-take-action-on-antimicrobial-resistance/).

2. Primary (principal) benefit

"Primary" benefit for people in Developing Countries must be fundamental in the design and impact of the project and are an explicit objective of the project.[20] This can be supported on several levels.

First, given the predominance of drug-resistant bacterial infections globally, the largest number of people who will benefit from most CARB-X funded investments will likely be residents of Developing Countries. While the surveillance data is not perfect, and is being improved by the WHO GLASS initiative and the Surveillance and Epidemiology of Drug-Resistant Infections Consortium (SEDRIC) program coordinated by Wellcome Trust, the best available data demonstrates that the primary population benefiting from investment in R&D for drug-resistant bacterial infections will be in Developing Countries.[21]

Fig 2. Graphical representation of AMR in developing countries included in the study.



Founou RC, Founou LL, Essack SY (2017) Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. PLOS ONE 12(12): e0189621. https://doi.org/10.1371/journal.pone.0189621
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0189621

Second, drug resistance today is undermining the effectiveness of dozens of antibiotics on the WHO Model List of Essential Medicines.[22] In the 2017 updates, essential antibiotics are for the first time classified into three groups: access, watch, and reserve. This was in response to the crisis of antibiotic resistance. For other types of products, similar approaches are appropriate. For example, the WHO recently published an Essential Diagnostics List[23] (note that diagnostics are not currently in scope for GAMRIF). A CARB-X applicant might intend for their device to eventually be added to future editions of that list. Similarly, a vaccine manufacturer might intend their vaccine to become GAVI eligible, meaning

[20] OECD (Development Assistance Committee). Converged Statistical Reporting Directives for the Creditor Reporting System (CRS) and the Annual DAC Questionnaire, par. 184 (8 Apr 2016) (available at https://www.oecd.org/dac/financing-sustainable-development/development-finance-standards/DCDDAC(2016)3FINAL.pdf).

[21] Tacconelli E, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018;317-27; WHO, Global Antimicrobial Surveillance System Report (2018); Theuretzbacher U. Global antimicrobial resistance in Gram-negative pathogens and clinical need. Curr Ops Microbiol 2017;39:106-112.

[22] World Health Organization, WHO Model List of Essential Medicines (20th ed., March 2017). The WHO also published the WHO Model List of Essential Medicines for Children (6th ed., March 2017).

[23] World Health Organization, WHO Model List of Essential In Vitro Diagnostics (1st ed., 16 May 2018).

the vaccine was prioritized for lower-cost distribution in Developing Countries.[24] For new alternatives to antibiotics, for which no such list is directly applicable, applicants should describe how the project should best fit into a category which might be analogous to these lists. In each case, the applicant relies on a global norm with clear benefit to Developing Countries.

Third, the World Health Organization, as a technical agency with expertise in the subject, convened an expert committee in 2017 to develop a Global Priority List of Antibiotic-Resistant Bacteria, explicitly to guide research and development decisions.[25] CARB-X has explicitly adopted this WHO Global Priority List as one of two threshold requirements for CARB-X funding (the other is the earlier 2013 CDC Priority List[26] as the WHO list had not been published when CARB-X was launched).

Fourth, some CARB-X awards are made to companies or research teams that have substantial presence in Developing Countries, including their headquarters, location of research facilities and CROs, and training of scientists and other professionals in Developing Countries.

Fifth, some CARB-X projects may include additional development requirements that are uniquely relevant to Developing Countries, including shelf stability, route of administration, cost of goods sold (to promote access), testing and efficacy against clinical strains more prevalent in Developing Countries, and other work to develop the product to be more useful in Developing Countries. We note that CARB-X funding comes during an early stage of development, beginning for therapeutics at hit-to-lead and ending with SAD/MAD phase 1 studies in humans. Most of the types of work described in this paragraph actually occurs in later development phases, after CARB-X funding is completed. As part of the CARB-X graduation process, product developers will be asked to describe their further plans to develop the product. In addition, as part of their contractual commitments to Stewardship and Access, all product developers will work with CARB-X during these later stages to support achievement of these goals.

Sixth, the CARB-X applicant may have other unique characteristics that demonstrate primary benefit to Developing Countries.

For a stronger case, the CARB-X applicant should express “primary benefit” through two or more of the following six categories:

a) The project can meet the first category with data suggesting successful action against one or more bacterial species that are prevalent in Developing Countries, based on available literature.
b) The second category can be met if the project intends to protect or replace a threatened antibiotic on the WHO Essential Medicines List or the WHO Essential Medicines List for Children.
c) Projects targeting bacteria on the WHO priority list should qualify under the third category, especially for the higher tiers on the WHO priority list.
d) All of the CARB-X award to companies with a footprint predominantly in Developing Countries should qualify under the fourth category; for companies with a substantial but not

[24] Https://www.gavi.org/.
[25] World Health Organization, Global Priority List of Antibiotic-Resistant Bacteria To Guide Research, Discovery, and Development of New Antibiotics (2017).
[26] US Centers for Disease Control and Prevention, Antibiotic Resistance Threats in the Unites States, 2013.

predominant footprint, perhaps only the funded activities that take place in Developing Countries should qualify if the applicant is relying solely on this fact to support "primary benefit."

e) As early-stage work, all CARB-X funding satisfies the fifth category, generally in combination with other supportive indicators from the other categories. If any later stage work is included in a CARB-X award that specifically addresses these issues (shelf stability, etc.), then that funding qualifies standing alone.

f) The sixth category allows a CARB-X applicant to make the case for primary benefit to Developing Countries in other ways.

3. Secondary (significant) benefit

Secondary (significant) benefit includes policy objectives that are not one of the primary reasons for undertaking the project.[27] A project may be ODA-eligible with one or more primary or secondary policy objectives,[28] including a secondary benefit to high-income countries, so long as the benefit to Developing Countries is primary.[29]

C. Primary intention

The CARB-X applicant must state that their "primary intention" in submitting the CARB-X application and execution of the proposed research is to achieve the two standards set out above. This needs to be justified with a statement that shows a "pathway to impact" (i.e., a development path that can eventually lead to positive health impact for people in DAC list countries), setting out why and how the work achieves the two standards set out above. Most CARB-X applicants are commercial enterprises, the boards of which are under fiduciary duties to shareholders. For a stronger case, the CARB-X applicant should express "primary intention" through two or more of the following five categories.

First, the great weight of evidence has established that antibiotic R&D suffers from market failures that would result in terrible consequences but for public and charitable support like CARB-X.[30] In that case, the only way to build an infrastructure to support Developing Country needs is to support these companies and research groups. Most CARB-X awards go to small and medium sized enterprises (SMEs). The only way to achieve scale in Developing Countries is to support CARB-X projects: the creation of a research and development program eventually leading to production of the product for Developing

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[27] OECD (Development Assistance Committee). Converged Statistical Reporting Directives for the Creditor Reporting System (CRS) and the Annual DAC Questionnaire, par. 185 (8 Apr 2016) (available at https://www.oecd.org/dac/financing-sustainable-development/development-finance-standards/DCDDAC(2016)3FINAL.pdf).

[28] OECD (Development Assistance Committee). Converged Statistical Reporting Directives for the Creditor Reporting System (CRS) and the Annual DAC Questionnaire, par. 187 (8 Apr 2016) (available at https://www.oecd.org/dac/financing-sustainable-development/development-finance-standards/DCDDAC(2016)3FINAL.pdf).

[29] Dr. Kate Hamer, Head of International, NERC. Official Development Assistance in the Research Context, slide 4 (undated) (available at https://nerc.ukri.org/research/partnerships/international/gcrf/news/workshop-outcomes/gcrf-workshop-kate-hamer/).

[30] See, e.g., Revitalizing the antibiotic pipeline: stimulating innovation while driving sustainable use and global access (The DRIVE-AB Final Report, 2018); AMR Review, Tackling drug-resistant infections globally: final report and recommendations (2016); WHA Global Action Plan (2015); UN Political Declaration on AMR (2016); World Bank, Drug-resistant infections (2017).

Countries would not be feasible for drug-resistant bacterial infections but for the infrastructure built to support sales in high-income countries.

Second, there is internal competition for capital within commercial firms. The CARB-X award supports the allocation of human and fiscal resources to projects that would not otherwise proceed. Developing Countries cannot benefit unless these projects result in actual products.

Third, the "primary intention" standard should not apply here to the entire company, but rather to the *primary intention for applying for CARB-X funding.* At the Expression of Interest stage, applicants are given a choice whether to pursue this route of funding or not. They are expressing intentionality with regard to this CARB-X application, not the other operations of the company. Note that as described above, the applicant can have more than one primary and secondary intentions.

Fourth, as described above, every CARB-X award comes with contractual conditions regarding antibiotic stewardship and global access. The global access provisions are primarily intended to benefit Developing Countries. Since CARB-X awards are entirely concessional (nondilutive with no equity or royalty), these are the primary *quid pro quo* required by CARB-X and applicants agree to these conditions primarily to benefit Developing Countries.

Fifth, the CARB-X applicant may express primary intention through other means.

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In conclusion, to qualify for ODA-eligible funds from GAMRIF through CARB-X, the applicant may use, as appropriate, the discussion above to set out the pathway to impact and to express their primary intention to promote the welfare and economic development of Developing Countries and benefit directly and primarily people in Developing Countries.

Annex: Information sources

Antibiotic resistance data sources

Global Antibiotic Resistance Partnership (GARP) data and reports https://cddep.org/partners/global-antibiotic-resistance-partnership, particularly their resistance map https://resistancemap.cddep.org

Global Antimicrobial Resistance Surveillance System (GLASS) Report: Early implementation 2016-17, which includes some LMIC country profiles with 2016 resistance data for key bacteria http://apps.who.int/iris/bitstream/handle/10665/259744/9789241513449-eng.pdf?sequence=1 and supplementary country data https://www.who.int/glass/resources/publications/early-implementation-report-supplementary-materials/en/

National Action Plans on antimicrobial resistance https://www.who.int/antimicrobial-resistance/national-action-plans/en/

Federation of Infectious Diseases Societies of Southern Africa publications list https://www.fidssa.co.za/SAASP/Publications

Gates Foundation Project: Antibiotic Resistance Situation Analysis and Needs Assessment (ARSANA) in Uganda and Zambia http://emerald.tufts.edu/med/apua/research/gates.shtml

Conducting health research in LMICs

The Global Health Network https://tghn.org includes a wealth of resources and good practice materials as well as online fora related to global health research

Clinical trials in LMICs

Global Health Trials platform https://globalhealthtrials.tghn.org

The European & Developing Countries Clinical Trials Partnership (EDCTP) http://www.edctp.org and related Knowledge Hub https://edctpknowledgehub.tghn.org

Pharma and vaccine company access issues

AMR Industry Alliance https://www.amrindustryalliance.org and its 2018 Progress Report https://www.amrindustryalliance.org/progress-report/

AMR Benchmark report 2018 https://amrbenchmark.org/wp-content/uploads/2018/04/Antimicrobial-Resistance-Benchmark-2018.pdf

Access to Medicines Index 2018 https://accesstomedicinefoundation.org/media/uploads/downloads/5c0e475363842_Access-to-Medicine-Index-2018.pdf

Access to Vaccines Index 2017 https://accesstovaccinesindex.org/media/atvi/2017-Access-to-Vaccines-Index.pdf