Request for Project Proposals

Solicitation Number: MTEC-17-01- Dengue Human Infection Model (DHIM) Prototype Development

Issued by:

Advanced Technology International,
MTEC Consortium Manager (CM)
315 Sigma Drive
Summerville, SC 29486
for the
Medical Technology Enterprise Consortium (MTEC)

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Noon Eastern Daylight Time

White papers Not Required

Table of Contents

1. Executive Summary

1.1. Purpose

The Medical Technology Enterprise Consortium (MTEC) is an enterprise partnership in collaboration with industry and academia to facilitate research and development activities, in cooperation with the U.S. Army Medical Research and Materiel Command (USAMRMC) and other Government agencies in the biomedical sciences (including but not limited to drugs, biologics, vaccines, medical software and medical devices) to protect, treat and optimize the health and performance of U.S. military personnel. MTEC is a nonprofit corporation with the following principal objectives:

(a) biomedical research and prototyping;

(b) exploration of private sector technology opportunities;

(c) technology transfer; and

(d) deployment of intellectual property (IP) and follow-on production.

MTEC is openly recruiting members to join a broad and diverse biomedical consortium that includes representatives from large businesses, small businesses, contract research organizations, "non-traditional" government contractors, academic research institutions and not-for-profit organizations; for more information on the MTEC mission, see the Proposal Preparation Guide (PPG) and MTEC website.

This solicitation, issued by the MTEC Consortium Manager (CM), Advanced Technology International (ATI), represents a Request for Project Proposals (RPP) for MTEC support of the U.S. Army Medical Materiel Development Activity (USAMMDA) and Military Infectious Diseases Research Program (MIDRP) technology objectives. Military relevance is a critical component of proposal submission. Strategic oversight for the award(s) supported by this RPP will be provided by USAMMDA.

Dengue viruses (DENVs) are flaviviruses transmitted by infected *Aedes* mosquitoes that cause a clinical spectrum of human disease ranging from mild viremia to severe intravascular volume depletion and hemorrhage. Efforts are underway worldwide to develop safe, effective anti-viral drugs and vaccines against Dengue but significant technical barriers impede progress including the immunologic complexity of the disease and lack of a correlate of protection or validated animal models of disease. Consequently, medical product developers must rely primarily on the conduct of large clinical studies in endemic regions (typically in pediatric volunteers) at great expense and financial risk.

The U.S. military Dengue Vaccine Program seeks to change this paradigm by co-developing a safe and reproducible Dengue Human Infection Model (DHIM). A successful DHIM will be a future enabling technology for DENV medical product developers and clinical researchers to: (i) test and predict efficacy of candidate vaccines, early chemoprophylaxis and anti-virals against DENV; (ii) identify and validate biomarkers of DENV disease progression for diagnosis, clinical care or epidemiology studies; (iii) compare or otherwise cross-reference the performance of different medical technologies or modalities in a U.S. Food and Drug Administration (FDA) regulated test and evaluation system; and (iv) elucidate the host response at the molecular level during uncomplicated DENV infection with the goals of understanding and controlling disease progression or identifying biological correlates of protection.

The DHIM represents an opportunity for consortium members and other qualified partners to reduce their overall risk during clinical development. For example, product developers may leverage the DHIM to explore pre-infection immune profiles and correlate results with post-experimental infection clinical

outcomes across a range of conditions and scenarios. It also may clarify how human humoral- and/or cellular-immune responses are associated with protection against DENV disease progression and, therefore, reduce the size and scope of future clinical trials and facilitate an improved use of existing laboratory animal models. In the long term, the DHIM could become a validated tool, recognized by the US FDA, to fill gaps in efficacy data from field studies and subsequently expedite licensure.

Military relevance is a critical aspect of this RPP. U.S. Service Members require an FDA-approved tetravalent DENV vaccine that is >80% efficacious. Despite development efforts over several decades, a vaccine suitable for use by the US Military has not been achieved. DENV vaccine development carries significant cost and schedule risk that may be reduced by development of an FDA-regulated, reproducible, safe DHIM. Military relevance includes the health care needs of Service members, Veterans, and/or other Military Health System beneficiaries; consequently, military medical needs often are also applicable to the civilian population.

1.2. Request for Project Proposals

This MTEC RPP is focused on accelerating ongoing development by USAMRMC of the DHIM, which aims to safely and reproducibly create uncomplicated dengue infections in human volunteers using live, attenuated, DENV challenge material. The DHIM will be achieved when each of the four DENV challenge strains (serotypes 1-4) is characterized via Phase 1 clinical studies.

To develop and implement a reproducible, well-characterized, FDA-regulated DHIM, this RPP specifically supports the establishment of a **team** of qualified partners that are prepared to share funding and in-kind resources or expertise and other tangible resources or expertise to support clinical trials, regulatory compliance and manufacturing of required materials. The team would be structured to permit future exchanges of characterized DENV challenge materials, clinical samples, assays or other DHIM commodities with other potential users and developers of DENV vaccines or therapeutics that meet US Military needs, including FDA licensure. The Government does not have adequate funding to completely fund the development of all 4 serotypes. It is expected that the team will actively pursue industry investment, grants or other funding sources to enable the full development of the DHIM.

Each MTEC research project proposal submitted must contain both a Technical and Cost Proposal Volume as described in Section 3 of this request and must be in accordance with the mandatory format provided in the MTEC PPG, which is available on the Members-Only MTEC website at www.mtec-sc.org. ***White papers are not required for this RPP.***

1.3. Funding Availability and Type of Funding Instrument Issued

The U.S. Government (USG) currently has planned approximately $3.4M per year in FY2018 and FY2019 and up to ~$1.3M per year in FY 21 and 22. As of the release date of this RPP, future year Defense Appropriations Bills have not been passed and there is no guarantee that any additional funds will be made available to support this program. The funding planned for this RPP is approximate and subject to realignment. Funding of proposals received in response to this RPP is contingent upon the availability of federal funds for this program.

Award funding will be structured incrementally and based upon completion of Milestones linked to implementation of each of the four DENV serotype-based modules and execution of the first performance validation study of DHIM-1; a study referred to herein as ADVP-005. Milestones do not have to be accomplished in a prescribed order and Offerors are encouraged to optimize schedule through the use of

concurrency or other approaches. Details of the key Milestones can be found in the Technology Objectives (RPP Section 3.2) and must include the following major tasks:

1) Establish IND for DHIM-2, DHIM-3, and DHIM-4 Challenge Materials. Devise and/or complete the Chemistry, Manufacturing, and Controls (CMC) section for the live, attenuated DENV-3, DENV-4 and DENV-2 challenge materials, in accordance with 21CFR312 standards and in accordance with eCTD standards as set forth in ICH M2. Provide completed CMC section to the USAMRMC for submission to the US FDA under IND 16332. Following submission, the USAMRMC will provide a Letter of Authorization (LOA), enabling the awardee to cross reference the USAMRMC DHIM IND (# 16332). Following development of each DHIM protocol (see items 2, 3, and and 5 below), become the sponsor of DHIM-3, DHIM-4 and DHIM-2 studies. The USAMRMC envisions that the Offeror will establish sponsorship through submission of the LOA and protocol (to the FDA) for each study and that the FDA, will assign an IND number, establishing the Offeror as the sponsor and, therefore, responsible for all duties commensurate with 21 CFR 312 subpart D, and ICH E6; and applicable FDA guidance and local regulations.

2) DHIM-3 Clinical Characterization. Develop and execute DHIM-3 clinical protocol and all required associated documents (e.g., Informed Consent Form (ICF), FDA 1571, FDA 1572, Investigators Brochure, (IB,), etc.) as necessary to conduct the study and as necessary to establish regulatory sponsorship with the FDA; execute DHIM-3 clinical protocol; acquire clinical trial execution support; implement all necessary services to comply with the regulations, guidance, and responsibilities commensurate with being the regulatory sponsor (as per item 1). Clinical services and clinical support services commensurate with sponsor responsibilities can be accomplished using intramural or CRO resources to carry out DHIM-3 to completion. Complete all activities to develop final report and close-out the DHIM-3 study.

3) DHIM-4 Clinical Characterization. Develop and execute DHIM-4 clinical protocol and all required associated documents (e.g., Informed Consent Form (ICF), FDA 1571, FDA 1572, Investigators Brochure, (IB,), etc.) as necessary to conduct the study and as necessary to establish regulatory sponsorship with the FDA. It is anticipated that the DHIM-4 protocol will be similar in design to the DHIM-3 protocol. Execute DHIM-4 clinical protocol; acquire clinical trial execution support; implement all necessary services to comply with the regulations, guidance, and responsibilities commensurate with being the regulatory sponsor (as per item 1). Clinical services and clinical support services commensurate with sponsor responsibilities can be accomplished using intramural or CRO resources to carry out DHIM-4 to completion. Complete all activities to develop final report and close-out the DHIM-4 study.

4) DHIM-2 Challenge Material. Partner with USG to scale-up, manufacture, vial and release DHIM-2 challenge material and develop CMC amendment (under IND 16332) for DHIM-2. **NOTE: The WRAIR Bioproduction Facility is currently unavailable due to renovations and, therefore, the Offeror must identify a suitable partner for DHIM-2 manufacturing.** USG (WRAIR) will provide subject matter expertise to facilitate manufacture of DENV-2. As research and development will be performed under US IND, manufacture of DENV-2 must be in accordance with (as applicable) 21CFR parts 210, 211, and 600, and applicable FDA Guidance for Industry (ex: CGMP for Phase 1 Investigational Drugs).

5) DHIM-2 Clinical Characterization. Complete and execute DHIM-2 protocol and associated documents (e.g., ICF, FDA 1571, FDA 1572, Investigators Brochure (IB), etc.) as necessary to conduct the study and as necessary to establish regulatory sponsorship with the FDA. Execute

DHIM-2 clinical protocol; acquire clinical trial execution support; implement all necessary services to comply with the regulations, guidance, and responsibilities commensurate with being the regulatory sponsor (as per item 1). Clinical services and clinical support services commensurate with sponsor responsibilities can be accomplished using intramural or CRO resources to carry out DHIM-2 to completion. Complete all activities to develop final report and close-out the DHIM-2 study.

6) Develop a Commercialization Plan that describes the strategy and teaming approaches the Offeror will employ to integrate efforts, maximize return-on-investment, and advance the DHIM through characterization studies so that it ultimately can be made available for use by a range of medical product developers (military and civilian) working toward FDA-regulated DENV countermeasures.

7) Perform a "field test" of the USAMRMC's characterized DHIM-1 challenge strain by assisting in the conduct of clinical study ADVP-005. In this study, the WRAIR's Alternate Dengue Vaccine Program (ADVP) candidate vaccine will be tested for efficacy using the characterized DHIM-1 challenge strain. The purpose of this study is two-fold: a) test the performance of the vaccine candidate against a defined inoculation challenge with characterized MRMC DENV-1 material; and b) provide an independent validation of the performance of DHIM-1 in a control group.

   In ADVP-005, the WRAIR Clinical Trials Center (CTC), Silver Spring, MD 20910 will function as the primary study center. Accordingly, it is mandatory that the Offeror-provided trial center is "local" (within 1 hour drive) to the WRAIR CTC. Volunteers in the experimental group(s) will be screened and enrolled at the CTC while volunteers in the control group will be screened and enrolled at the Offeror's site. The Offeror will serve as the study Sponsor with sponsorship established via Government provision of an LOA (as above).

   The ADVP-005 trial will incorporate the following design elements:

   Experimental group: Volunteers will visit the WRAIR CTC for vaccination and subsequent inoculation with DHIM-1 challenge material. After inoculation, subjects will be contacted by phone until they display dengue symptoms. Upon detection of dengue symptoms by the WRAIR CTC study team, the CTC PI will refer the subject to the Offeror's PI. The Offeror is expected to provide for transportation of the volunteer to their site. Offeror will provide in-patient care of volunteer(s), in accordance with protocol procedures, until release criteria are met. Once released, volunteers will be referred to the WRAIR CTC PI and followed until conclusion of the study. Offeror shall also provide for volunteer transportation back to their residence.

   Control Group: The contractor shall screen and enroll volunteers for the control group, following full protocol procedures. Please note that it is anticipated that 100% of the volunteers in the control group will contract a mild, uncomplicated dengue illness.

MTEC anticipates that a single award will be made to a qualified team composed of multiple investigators/institutions responsible for partnering with the USG to accomplish all tasks. However, if an optimal team is not identified, then MTEC may make multiple, individual awards to Offeror(s) to accomplish subset(s) of the key tasks.

The Government-selected Research Project Awards will be funded under the Other Transaction Agreement (OTA) Number W81XWH-15-9-0001 (or subsequent OTAs in support of MTEC) with MTEC administered by the CM, ATI. The CM will negotiate and execute a Base Agreement with MTEC members. This Base Agreement will be governed by the same provisions as the OTA between the USG and MTEC. Subsequently, any proposal that is selected for award will be funded through a Research Project Award issued under the Base Agreement. A sample of the MTEC Base Agreement can be found on the Members-Only MTEC website at www.mtec-sc.org.

At the time of the submission, if Offerors have not yet executed a Base Agreement, then Offerors must certify on the cover page of their proposals that, if selected for award, they will abide by the terms and conditions of the latest version of the MTEC Base Agreement. If the Offeror already has executed an MTEC Base Agreement with the MTEC CM, then the Offeror must state on the cover page of its proposal that, if selected for award, it anticipates the proposed effort will be funded under its executed MTEC Base Agreement.

Offerors are advised to check the MTEC website periodically during the proposal preparation period for any changes to the MTEC Base Agreement terms and conditions as well as clarifications found in Frequently Asked Questions (FAQ) responses.

1.4. Proprietary Information

The MTEC CM will oversee submission of proposals and analyze cost proposals submitted in response to this RPP. The MTEC CM shall take the necessary steps to protect all proprietary proposal information and shall not use such proprietary information for purposes other than the evaluation of an Offeror's proposal and the subsequent agreement administration if the proposal is selected for award. An Offeror's submission of a proposal under this RPP indicates concurrence with the aforementioned CM responsibilities. MTEC CM responsibilities. Also, as part of MTEC's mission to incorporate philanthropic donations, MTEC frequently makes contact with private foundations that award grants for research and operate in research areas that are aligned with those of MTEC. These private foundations may be interested in reviewing proposals within their program areas, allowing for opportunities to attract supplemental funding sources. On your proposal Cover Page, please indicate your willingness to allow MTEC Officers access to your Technical Proposal for the purposes of engaging in outreach activities with these private foundations. MTEC Officers granted proposal access have signed Nondisclosure Agreements (NDAs) and Organizational Conflict of Interest (OCI) statements. Additionally, these MTEC Officers represent organizations that currently are not MTEC members, and therefore their parent organizations are not eligible to submit research project proposals, nor receive any research project funding through MTEC.

1.5. Offeror Eligibility

Offerors must be MTEC Members in good standing.

1.6. Inclusion of Non-traditional Defense Contractors

Proposals that do not include Non-traditional Defense Contractor participation to a significant extent, or do not propose at least one third acceptable cost sharing, will not be eligible for award. Please see the MTEC PPG and RPP Section 4, for additional details.

1.7. Cost Sharing

Cost sharing is defined as the resources expended by the award recipients on the proposed statement of work (SOW). *The extent of cost sharing is a Factor in the evaluation of proposals (RPP Section 4.1).* If cost

sharing is proposed, then the Offeror shall state the amount that is being proposed and whether the cost sharing is a cash contribution or in-kind contribution, a description of each cost share item proposed, the proposed dollar amount for each cost share item, and the valuation technique used (e.g., vendor quote, historical cost, labor hours and labor rates, number of trips, etc.) for each cost share item.

See the MTEC PPG for additional details. If the offer contains multiple team members, this information shall be provided for each team member providing cost share.

For additional information regarding Non-traditional Defense Contractors and Cost Sharing, please see the Cost Share Guidance document available on the Members-Only portion of the MTEC website www.mtec-sc.org.

1.8. Intellectual Property

Intellectual Property (IP) rights for MTEC Research Project Awards will be defined in the terms of an awardee's Base Agreement and resultant Task Orders. MTEC reserves the right to assist in the negotiation of IP, royalties, licensing, future development, etc between the government and the individual performers during the entire award period.

Per Section 3.4 of the Consortium Member Agreement (CMA), each recipient of a research project award under the MTEC OTA shall pay MTEC an amount equal to 1% of the total funded value of each research project award. Such deposits shall be due no later than 90 days after the research project award is executed. Awardees are not allowed to use MTEC funding to pay for their assessment fees. Additionally MTEC has established two methods of payment to be made to MTEC surrounding the licensing/commercialization of Intellectual Property developed with funding received from MTEC Research Project Awards. MTEC has established two methods of payment to be made to MTEC surrounding the licensing/commercialization of Intellectual Property developed with funding received from MTEC research project awards:

Each awardee will select either the MTEC Additional Research Project Award Assessment or the Royalty Payment Agreement, not both, at the time of proposal preparation. Either a signed MTEC Additional Research Project Award Assessment or signed Royalty Payment Agreement must accompany your proposal submission. Summary explanations of each are provided below.

- Royalty Payment Agreement – Government-funded research projects awarded through MTEC will be subject to a 10% royalty on all Net Revenues received by the research project award recipient resulting from the licensing/commercialization of the technology, capped at 200% of the Government funding provided.

- In lieu of providing the royalty payment agreement described above, members receiving research project awards may elect to pay an additional assessment of 2% above the standard assessment percentage described in Section 3.4 of the CMA. This additional assessment applies to all research project awards, whether the award is Government funded or privately funded.

1.9. Expected Award Date

Offeror should plan on the period of performance beginning **October 15, 2017,** (subject to change**)**. The Government reserves the right to change the proposed period of performance start date through negotiations via the CM and prior to issuing a Research Project Award.

1.10. Anticipated Proposal Selection Notification

As the basis of selections are completed, the Government will forward their selections to the MTEC CM to notify Offerors.

2. Full Proposal

2.1. Full Proposals

Full Proposals in response to this RPP, must be received by the date on the cover page of this RPP. Proposals received after the time and date specified will not be evaluated.

The MTEC PPG is specifically designed to assist Offerors in understanding the proposal preparation process. The proposal format provided in the MTEC PPG is mandatory. MTEC will post any general questions received and corresponding answers (without including questioner's proprietary data) on the Members-Only MTEC website.

2.2. Proposal Submission

Offerors must submit proposals via email to Mtec-contracts@ati.org.

2.2.1. Submission Format

Offerors should submit files in Microsoft Office formats or Adobe Acrobat (PDF – portable document format) as indicated below. ZIP files and other application formats are not acceptable. All files must be print-capable and without a password required. Filenames must contain the appropriate filename extension (.docx, .doc, .pptx, .ppt .xlsx, .xls or .pdf). Filenames should not contain special characters. Apple users must ensure the entire filename and path are free of spaces and special characters.

- **Full technical proposal submission:** one Word (.docx or .doc) or PDF file. Separately, a Word (.docx or .doc) version of the SOW (Appendix B of the proposal) is required.

- **Full cost proposal submission:** one Word (.docx or .doc) or PDF file for Section I: Cost Proposal Narrative required. Separately, Section II: Cost Proposal Formats either in Excel (.xlsx or .xls) or PDF format is required.

- **Warranties and Representations:** If Non-traditional Defense Contractor participation is proposed, Warranties and Representations are required. One Word (.docx or .doc) or PDF file that contains all Warranties and Representations is required.

MTEC will email receipt confirmations to Offerors upon submission of proposals. Offerors may submit proposals in advance of the deadline.

3. Proposal Preparation Instructions

3.1. General Instructions

The Technical Proposal and Cost Proposal must be submitted in two separate volumes, and shall remain valid for 180 days unless otherwise specified by the Offeror in the proposal. The proposal format provided in the MTEC PPG is mandatory. Proposals shall reference this RPP number (MTEC-17-01-Dengue Human Infection Model).

Offerors are encouraged to contact the POC identified herein up until the proposal submission date/time to clarify requirements. Offerors are to propose a Milestone Payment Schedule which should include all significant event/accomplishments that are intended to be accomplished as part of the project, a planned completion date (based on months post award), the expected research funding expended towards completing that milestone, and any cost share, if applicable. The Milestones and associated accomplishments proposed should, in general, be commensurate in number to the size and duration of the project. A milestone is not necessarily a physical deliverable; it is typically a significant R&D event. Quarterly and final technical reports may be considered deliverables, but they are not milestones. Please include quarterly and final technical reports as part of the Milestone Payment Schedule, without an associated cost.

All eligible Offerors may submit proposals for evaluation according to the criteria set forth herein. Offerors are advised that only ATI as the MTEC CM, with the approval of the Government Agreements Officer, is legally authorized to contractually bind or otherwise commit funding for selected Research Project Awards as result of this RPP.

3.2. Technical Proposal

3.2.1. Technology Objectives

The overall technology objective is to develop a safe, reproducible DHIM for each of the four circulating DENV serotypes based on well-characterized challenge materials; to foster collaborative future use of the DHIM; and to share resulting clinical data, results, and clinical samples among qualified contributing partners.

MTEC encourages partnerships that pool available funding and in-kind contributions toward developing and characterizing a modular, serotype-based DHIM that can be made available to advance the field of DENV vaccines and therapies.

The DHIM is based on threshold-level exposures to live, attenuated strains of DENV ('challenge material') under controlled clinical conditions to create mild, uncomplicated dengue illness in human volunteers. The US Army and partners have initiated characterization of challenge material under an FDA-regulated Investigational New Drug (IND) effort (IND No. 16332) and have designed and undertaken a clinical trial examining DENV serotype 1 (Clinical trials identifier NCT02372175. This MTEC award will focus on the development of DENV-3, DENV-4, and DENV-2 challenge material and an efficacy “field test” of WRAIR’s ADVP dengue vaccine candidate using the characterized DHIM-1 challenge material (referred to herein as clinical study ADVP-005).

Successful Offerors will expand the DHIM development efforts to characterize available clinical-grade challenge materials for DENV serotype 3 and 4 in small, FDA-regulated phase 1 studies (note: Offerors

should take approaches that result in quantifiable economies of scale); co-develop more efficient methodologies for clinical characterization of challenge materials; develop, produce, and characterize DENV 2 challenge material; field test the characterized DHIM-1 challenge material in ADVP-005; and ultimately maintain the products of the DHIM, including DENV challenge materials, ex vivo clinical samples, and validated clinical methods, as commodities to share or exchange among qualified team-members and other qualified partners.

Offerors should note that specific technology objectives below are linked to the expansion of past and ongoing efforts of the USG and, consequently, are anticipated to involve teaming arrangements with government furnished materials and information shared through appropriate in-kind exchanges and partnership agreements. Please refer to the list of potential materials that can be made available to successful Offeror(s) (Section 3.2.3 Government Furnished Resources), Supplementary Technical Material (Section 3.2.4), as well as the PPG and MTEC website for additional details.

1. **Specific Technology Gaps**: Proposals and Statement of Work should address the Technology Objectives by proposing solutions to the following specific technology gaps and requirements in the context of the existing DHIM technology baseline outlined herein:

i. Devise and/or complete the CMC section for the DENV-3, DENV-4 and DENV-2, in accordance with 21CFR312 standards and in accordance with electronic Common Technical Document (eCTD) standards as set forth in ICH M2. Provide completed CMC section to the USAMRMC for submission to the US FDA under IND 16332. Following submission, the USAMRMC will provide a LOA, enabling the awardee to cross reference the USAMRMC DHIM IND (# 16332). Following development of each DHIM protocol (see items ii. and iv. below), **become the regulatory sponsor** of DHIM-3, DHIM-4 and DHIM-2 studies. The USAMRMC envisions that the Offeror(s) will establish sponsorship through submission of the LOA and protocol (to the FDA) for each study and that the FDA, using will assign an IND number, establishing the Offeror as the sponsor and therefore responsible for all duties commensurate with 21 CFR 312 subpart D and ICH E6; and applicable FDA guidance and local regulations. **Successful Offeror(s) must have the necessary capabilities to assume the role of sponsor for these FDA-regulated IND studies** and (in general) sponsorship of efforts of the size and scope required for clinical characterization of DHIM challenge materials. (Note: Each CMC section / IND amendment should be treated as separate “regulatory modules” within the submitted budget).

Offerors should provide an institutional letter of support to demonstrate acceptance of senior institutional leadership and institutional review boards to perform efforts of this risk profile, size, and scope.

We anticipate that Offerors will use the established Clinical Data Management System (CDMS) currently being utilized for the DHIM-1 study (and provided by the USG) for the DHIM-2, DHIM-3, DHIM-4, and ADVP-005 clinical studies.

MTEC anticipates the Offeror will continue to use the Walter Reed Army Institute of Research (WRAIR) Viral Diseases Branch for performing flavivirus screening tests as well as quantitative viremia testing via PCR methods.

The USG has an established contract for Data Safety Management Board (DSMB) support with Cherokee Nations Assurance. The existing DSMB contract is capable of supporting each of the four clinical

characterization studies (DHIM-1, 2, 3, and 4). MTEC anticipates that the Offeror will continue to use the established DSMB support contract. However, Offerors may choose to propose alternative arrangements for completion of the follow-on DHIM studies.

ii. Devise and submit to the FDA the LOA, the clinical protocol (and related documents), and other documents (as necessary) to enable the clinical evaluation of available DENV-3 challenge material and complete clinical characterization, proposed post-characterization activities and implementation of the DHIM-3 clinical trial module.

iii. Devise and submit to the FDA the LOA, the clinical protocol (and related documents), and other documents (as necessary) to enable the clinical evaluation of available DENV-4 challenge material and complete clinical characterization, proposed post-characterization activities and implementation of the DHIM-4 clinical trial module.

iv. Partner with U.S. Army to manufacture, in accordance with current Good Manufacturing Practices (cGMP), clinical grade live, attenuated DENV-2 challenge material. Strain selection for DENV-2 challenge material is currently in down-selection studies (using non-human primates, NHP) at WRAIR. After selection, the Sponsor would facilitate transfer of necessary data to manufacture clinical-grade DENV-2 challenge material for DHIM-2.

v. Devise and submit to the FDA the LOA, the clinical protocol (and related documents), and other documents (as necessary) to enable (based upon future production of DENV-2 challenge material) clinical characterization, proposed post-characterization activities and implementation of the DHIM-2 clinical trial module.

vi. Partner with U.S. Army to devise and submit to the FDA all required documents including the LOA, the clinical protocol, and supporting documentation necessary to enable FDA-regulated “field testing” of the USAMRMC’s ADVP dengue vaccine candidate in a clinical challenge study to be conducted at the WRAIR CTC and the Offeror’s site; devise, execute and analyze the results of the ADVP-005 clinical trial module.

2. **Clinical Plans for Characterization of Challenge Material.** Each of four DENV strains must be tested to demonstrate it can safely and reproducibly create a mild, un-complicated dengue infection at the lowest possible exposure dose under rigorously controlled clinical conditions that protect human subjects. DHIM clinical characterization is comparable with that required for vaccine candidates undergoing FDA-regulated Phase 1 clinical trials.

For DENV-3, DENV-4 and DENV-2 challenge materials, and the ADVP-005 clinical study, the Offeror's plan should cover all necessary activities to complete clinical characterization, including all responsibilities commensurate with regulatory sponsorship including (but not limited to) safety reporting and pharmacovigilance, clinical monitoring, data management, regulatory writing and submissions, stability reporting, DSMB support with consideration to use of existing USAMMDA-held DSMB contract,, and biostatistics as per sponsor responsibilities under ICH E6, E2A, E8, and 21 CFR parts 312, 11, 50, 54, 56. Of note, the Offeror will be the FDA regulatory sponsor of the DHIM-2, DHIM-3, DHIM-4, and ADVP-005 studies and will be required to execute all duties commensurate with that designation.

Clinical plans shall be integrated with all Program Management tools including the draft IMP, IMS, RMP, and Regulatory Plans and should clearly communicate the Offeror's approach to fulfill sponsor responsibilities (e.g. in-house clinical trial assets and/or CRO-managed partnerships).

An optional checklist to assist Offerors in developing the Clinical Plan is provided as Supplementary Technical Material to this RPP.

Clinical Plans should provide adequate technical details of proposed clinical protocol design(s), key personnel, clinical facilities, proposed clinical procedures, supporting laboratory studies, and post-characterization data analysis including but not limited to the following:

i. **Clinical Protocols.** Offerors are advised to consider the general approach used in the ongoing DHIM-1 clinical trial (see Section 3.2.4 Supplementary Technical Materials for a copy of the pre-IND meeting minutes). Offerors may propose modifications to the approach taken for the characterization of DENV-1 clinical protocol for DENV-3, 4, and 2, consistent with risk-based assessments that may accelerate the plan or enhance its efficiency with respect to cost or schedule. Offerors should consider approaches that maximize economies of scale to reduce overall costs for the USG.

ii. **Clinical Capabilities and Clinical Support Setting.** Clinical Plans should describe capabilities including key regulatory personnel. Key personnel should include a senior Regulatory Affairs Advisor, Principal Investigator (PI) and Associate Investigator(s) who are experienced in the care and treatment of individuals infected with dengue virus and/or experienced in designing and conducting infectious diseases human challenge studies.

Clinical Plans also should include appropriate details of the relevant support staff qualifications, capabilities and outpatient facilities for the proposed clinical trial site(s), ancillary out-patient clinical support settings, and any relevant biomedical laboratories or related facilities.

Offerors are advised that clinical trial sites and clinical support settings are limited to the continental United States, ideally in a geographical area lacking a pervasive presence of the DENV Aedes albopictus or Aedes aegypti mosquito vector. Alternative geographical areas will be considered if Offeror provides an appropriate vector transmission risk mitigation plan.

iii. **Importance of Volunteer Protections.** Primary infections in otherwise healthy, flavivirus-naive adults are rarely associated with severe clinical complications but clinical plans must clearly address this possibility in terms of the clinical risk reduction approach to address hemorrhagic features of DENV infection.

Clinical Plans shall describe planned controls to safeguard subject health and prevent unintentional DENV disease transmission and progression during implementation of a human disease challenge/infection model. The plans should address physical/technical safeguards (including but not limited to clinical and laboratory assessments) to ensure volunteer outcomes and prevent unintentional spread.

Clinical protocols should account for monitoring signs and symptoms of DENV infection that a DHIM would need to replicate in otherwise healthy adults including fever, headache, myalgia, musculoskeletal pain, and nausea or vomiting.

Clinical protocols also should describe data collection in terms of known features of viral infection (e.g., duration of viremia, thrombocytopenia, leukopenia or clotting abnormalities) and potential exploratory assays that could be conducted either through the WRAIR or by other consortium partners.

iv. **Data Management Plan.** Offerors are advised that MTEC can coordinate requests from successful Offerors to access and use of the existing USAMMDA CDMS (see Section 3.2.3 Government Furnished Resources). While Offerors are expected to use the USAMMDA CDMS for DHIM-4 and DHIM-2 studies, Offerors may propose using, adapting, or replacing the USAMMDA CDMS.

v. **Clinical Monitoring.** Offerors should describe a risk-based approach to clinical monitoring to ensure the protocol(s) are conducted in accordance with the principles of ICH E6, FDA GCPs, and requisite portions of 21CFR. Deliverables anticipated from the successful Awardee for this activity include a clinical monitoring plan(s), clinical monitoring visit reports for each study, and corrective action tracking/reports adequately demonstrating management and resolution of any observed protocol non-conformance. Additionally, the clinical Monitors are expected to conduct site-initiation visits (SIV), for cause visits, and closeout visits.

vi. **Sample Analysis, Archival and Dissemination.** Offerors should describe any specific clinical- and post-characterization plans to collect, analyze, store, maintain and otherwise exploit ex vivo clinical samples from the DHIM clinical studies to find reliable biological markers for the kinetics of human infection and for the development of potential correlates of protection. Offerors should (where applicable) describe a teaming approach to address such exploratory analysis.

Offerors should describe plans to incorporate processes to develop and archive appropriate DHIM clinical data and results employing methods for data capture that will be consistent with future use of the DHIM modules by other qualified partners. For example, other MTEC DHIM team members, including USG or other pre-qualified partners may seek to apply the clinical methods, data and results developed under this RPP to evaluate the performance of vaccine/drug candidates and (in parallel) to further characterize the safety and performance of the DHIM strains.

vii. **Data Safety Monitoring Board (DSMB)**. Offerors may use the existing USAMMDA-held DSMB contract for completion of the DHIM-2 and 4 clinical trials. Offerors alternatively may propose using, adapting, or replacing the USAMMDA DSMB contract. Offerors should describe, in general, a proposed DSMB structure and time points at which the DSMB will meet to review trial data.

viii. **Safety and Pharmacovigilance**. Commensurate with the satisfying regulatory obligations as the Sponsor of a clinical study, the Offeror(s) must establish and maintain a function to perform required safety reporting and pharmacovigilance for each study performed.

3. **DHIM Challenge Material.** Offerors are advised that the US Army already has completed preclinical tests, manufactured, vialed and released DHIM challenge material for DENV serotypes 1, 3 and 4 in accordance with Good Manufacturing Process (cGMP) guidelines (see 3.2.3 Government Furnished Resources).

The DENV-3 challenge material has an approximately one-half complete CMC. The DENV-4 challenge material has an approximately one-third complete CMC. The awardee will be provided with completed

content (upon request) to facilitate expeditious completion of the CMC; the completed CMC subsequently will be provided to the Government for submission to the FDA under the Government's DHIM IND 16332.

DENV-2 challenge strain is at an earlier stage of technology development. Offerors may propose cost-sharing partnerships that support or enhance government-led down-selection of DENV-2 strains, testing of cell banks, testing for adventitious agents and preparation of clinical-grade, vialed material.

DENV-1 challenge strain is currently being characterized in a phase 1 study. Following successful completion of that characterization study, DENV-1 challenge material will be utilized by the Offeror to inoculate control group subjects I the ADVP-005 study. The Government will provide DHIM-1 challenge material in quantities adequate to enable the Offeror to meet the needs of the protocol.

Offerors shall propose plans to monitor stability and manage DHIM challenge materials used for FDA-regulated clinical characterization studies. This may involve coordination with the Government for continuation of status quo storage at WRAIR, Forest Glen, MD, or a well justified transition plan from the government facilities to a suitable alternate site; prepare necessary regulatory submission packages; maintain product stability reporting and other documentation required to meet FDA regulations.

3.2.2. Program Management Requirements

Offerors must describe their proposed Program Management (PM) Approach to achieving the Technology Objectives including any key PM personnel. Proposals must address the following key PM tools and elements:

1. Integrated Master Plan (IMP), Integrated Master Schedule (IMS) and Risk Management Plan (RMP): Offerors shall provide a draft IMP, IMS and RMP for the proposed project describing an over-arching, time-phased project plan to devise and prototype the DENV-3, 2 and 4 components of the DHIM and to conduct ADVP-005 (total time not-to-exceed four years post-award). The IMP, IMS, and Offeror's SOW should be structured to correlate with each other (see the MTEC PPG for more information on preparation of the SOW).

The IMP should identify the proposed transition points and source(s) for all key clinical reagents and assays anticipated for implementation of the prototype DHIM; include in-kind tangible contributions of dollars; and propose a general time-table for technology transition from USG to Offerors for project completion.

The RMP should detail the Offeror's methods for identifying, analyzing, prioritizing, mitigating, and tracking key risk drivers; identify adequate resources for risk mitigation strategies to demonstrate the understanding of a sound risk management system; include a risk/benefit matrix for exposure of naive subjects to DENV; and describe implementation of a risk-reduction strategy to protect and treat clinical subjects exposed to DENV challenge materials. Additionally, Offerors should describe methodology for defining, mitigating, and managing project associated risks that could impact cost, schedule, and performance.

Plans do not have to conform to specific format but should depict the logical flow, proposed schedule and key decision points for development (clinical characterization) and implementation (post-characterization activities) for DHIM modules covering each of the four circulating DENV serotypes.

*2. Regulatory Plan and Quality Management Plan*s: Offerors should propose an overall Regulatory Strategy and the draft Regulatory Plan that will be used to achieve and manage the strategy. The Regulatory Plan maps resources to the regulatory requirements in the SOW and other sections of the solicitation, including adherence to FDA regulations, guidance, and the requirements related to development, manufacturing and testing of components of the DHIM. The proposed Regulatory Strategy and Regulatory Plan should be consistent with and align to the proposed IMP/IMP including appropriate milestones, decision points and risk mitigation steps.

Offerors should include a draft Quality Management Plan for any proposed CRO efforts demonstrating the Offeror has an effective Quality Management System that describes in sufficient detail the approach to Quality Assurance and Quality Control (QA/QC) and all significant subcontractors' QA/QC. The Offeror shall demonstrate compliance with FDA quality requirements or the approach to becoming compliant.

3. Resource Integration Plans/Teaming Arrangements: Offerors should propose their plan(s) for teaming, co-development opportunities, management of DHIM resources (DENV challenge materials, clinical samples, protocols, methods and results, etc.) as well as their approach to sharing resources across a wider consortium of DENV researchers and other potential qualified partners.

Offerors are strongly encouraged to provide letters-of-intent or similar collaborative commitments from teaming partners that document planned support or clarify the Offeror's teaming arrangements, as appropriate.

4. Commercialization Plan: Offerors shall submit a mandatory Commercialization Plan that describes the strategy the Offeror will employ to advance the DHIM through characterization studies so that it can be made available for use by developers (military and civilian) of dengue countermeasures. The Commercialization Plan should provide a roadmap to convey how the Offeror and government may ultimately generate return-on-investment and/or recover development costs. In doing so, Offerors should also consider acquired DHIM volunteer samples as potentially valuable research commodities.

Offerors may use the Commercialization Plan as an opportunity to propose to co-develop modules of the DHIM in the context of studies of specific medical solutions (e.g., proprietary vaccines or anti-viral therapeutics) using in-kind resources provided by the Offeror. In such cases, Offerors are advised that the primary focus of the RPP is the development of the DHIM and any plans to co-develop the model in the context of other technologies must ensure the DHIM, and/or associated IP for the DHIM, remains sufficiently unencumbered to facilitate its use by all DHIM team participants and other qualified commercial partners; such that the USG can achieve its mission of delivering dengue countermeasures to US Service Members.

Assumptions within the Plan should be clearly stated and include pertinent information about IP. For more information on the Commercialization Plan requirements, please refer to the MTEC PPG. The Commercialization Plan should concisely convey:

i. Business opportunity enabled by the DHIM modules and the compelling value proposition for the intended customer(s). For example, Offerors might address how DENV challenge material would be marketed to potential commercial partners as a business opportunity; development of possible pricing structures; and how use of DHIM resources, including the challenge materials, will be managed such that intellectual property remains un-encumbered.

ii. Realistic understanding of the current and anticipated marketplace in the context of global humanitarian efforts to control DENV. The DHIM prototype is envisioned as a collective clinical research tool that ultimately will be made available to multiple product developers without undue restriction. Consequently, plans are sought that provide for sharing DHIM methods and reagents widely across a global consortium of qualified DENV vaccine and therapeutics researchers while concurrently ensuring the technical rigor and reproducibility of the underlying methodology and results.

iii. Methods to develop and protect new IP that may arise during DHIM characterization, including methods and critical reagents; this includes any anticipated method-use claims re-purposing government-furnished Live Virus Human Challenge (LVHC) attenuated DENV strains as challenge material. LVHC strain formulations are currently protected by USPTO patents held by the U.S. Army (see Section 3.2.4 Supplementary Technical Material).

3.2.3. Government Furnished Resources

Project proposals to meet the Technology Objectives may assume that the government will make available the following materials and information as part of successful DHIM contract award:

1. A LOA enabling the successful Offeror to cross-reference the existing USAMRMC DHIM IND # 16332 and (subsequently) establish Sponsorship for DHIM-3, 4 and 2 studies. A LOA will also be provided to enable the Offeror to cross reference IND # 16122, thus enabling sponsorship of the ADVP-005 study. We will provide assistance to the successful Offeror in the establishment of regulatory sponsorship for the DHIM-3, 4 and 2 DHIM clinical studies by cross-reference of the USAMRMC DHIM IND (#16332) and for ADVP-005 through cross-reference of the USAMRMC IND (# 16122). We also will enable cross-reference to IND 16332 as required for post-characterization vaccine and/or drug challenge studies employing the DHIM challenge materials.

Establishment of regulatory sponsorship for the DHIM-2, 3 and 4 studies is envisioned to occur through provision of a LOA(s) from MRMC. It is anticipated that the successful Offeror(s) will subsequently establish regulatory sponsorship through subsequent submission of the LOA and protocol package, including protocol package,(but not limited to): Clinical Trial Agreement (CTA), Informed Consent Form (ICF), Investigator's Brochure (IB), FDA forms 1571 and 1572, and other documents (as necessary) to conduct the clinical trials. For this sake of clarity, it is required that the successful Offeror(s) establish their institution as the regulatory sponsor for all studies herein. However, the Government will consider mechanisms other than the LOA mechanism described above.

2. The DENV-LVHC serotypes 1, 3 and 4 were manufactured, vialed, and stored under clinical-grade conditions for the original purpose of experimentally inoculating human volunteers and are currently being evaluated under the aforementioned, ongoing FDA-regulated IND 16332 clinical characterization study. The DENV-LVHC strains are not intended as routine vaccines but rather are envisioned as critical reagents that may serve Offeror(s) as reproducible, live attenuated virus challenge strains in development of their proprietary vaccine or drug (therapy or prophylaxis) candidates. Additional technical details of the quantities and formulation for the existing vialed reagents will be made available to Offerors as RPP Supplementary Material.

DHIM Dengue Challenge Strain Materials: We will make available sufficient quantities of vialed, live-attenuated, monovalent strains of dengue virus serotype 3 (DENV-3- LVHC), serotype 4 (DENV-4- LVHC) for completion of the DHIM-3 and DHIM-4 clinical characterization studies by successful Offeror(s). We will also make available, in sufficient quantities to satisfy protocol needs, DENV-1-LVHC for tha ADVP-005 study. Vialed challenge material is stored at WRAIR, Forest Glen, MD.

3. Documentation and technical cognizance describing ongoing government efforts at WRAIR to down-select strains to assist Offerors in developing and manufacturing comparable, clinical-grade challenge material for the live-attenuated, monovalent strain of DENV serotype 2 (DENV-2- LVHC vaccine strain). Partners interested in cost-sharing for the manufacturing of DENV-2 should indicate their approach to co-develop DHIM-2 in the proposal IMP/IMS.

4. Available DHIM protocols and methodologies. The Funding Sponsor will provide the successful Offeror(s) with available government-furnished documentation and laboratory protocols supporting the performance of DHIM clinical assays (as necessary); including: flavivirus screening assays, qualitative PCR, and quantitative PCR-based laboratory assays.

DENV propagation and clinical inoculation methods support the use of government-furnished DENV-LVHC challenge strains. WRAIR has developed PCR-based detection assays that can assist successful Offeror(s) with the ability to screen clinical subjects as part of exclusion criteria, and/or validate the occurrence or clearance of DENV during and immediately following clinical studies. Qualitative PCR assays will need to be transferred to all participating DHIM clinical sites.

MTEC anticipates that Offerors will continue to use the WRAIR to perform flavivirus screening and quantitative PCR assays but alternate assay sites may be proposed. Qualitative PCR methods will be transferred by WRAIR staff to active clinical site(s); the PCR assay is currently required by clinical protocol under IND 16332 before releasing volunteers from in-patient care.

5. Access to government-furnished resources of the current DSMB (contractor operated) and the USAMMDA CDMS. These resources can assist successful Offeror(s) in conducting protocol safety reviews, as well as in the systematic capture and maintenance of clinical data in formats appropriate for FDA-regulated clinical characterization studies in support of the DHIM.

The USG will facilitate post-award negotiations and collaboration between the successful Offeror(s) and existing USG-contractors for utilizing the existing USAMRMC-held DSMB support contract and the USAMRMC CDMS.

3.2.4. Supplementary Technical Material

The following Supplementary Technical Materials will be made available upon execution of the MTEC Non-Disclosure Agreement (NDA) to assist in RPP proposal preparation. The NDA will be posted on the MTEC Members-Only Website.

1. Pre-IND Meeting Background Information for FDA-TSG, Department of the Army meeting on CRMTS 9523 "DENV-1-LVHC Dengue-1-Virus-Live Virus Human Challenge (DENV-1-LVHC) Development of a Dengue Human Infection Model (DHIM): Assessment of a DENV-1-LVHC Virus Strain, " dated Nov. 10, 2014
2. DHIM Risk Assessment Matrix

55. List of Relevant Patents/ Intellectual Property

3.2.5. Restrictions on Human Subjects, Cadavers, and Laboratory Animal Use

Technical proposals must comply with important restrictions and reporting requirements for the use of human subjects, to include research involving the secondary use of human biospecimens and/or human data, human cadavers, or laboratory animals. For a complete description of these mandatory requirements and restrictions and others, Offerors must refer to the accompanying MTEC PPG, Section 6.11 Additional Requirements.

These restrictions include mandatory government review and reporting processes that will impact the Offeror's schedule.

For example, the clinical studies under this RPP shall not begin until the USAMRMC Office of Research Protections (ORP) provides authorization that the research may proceed. The USAMRMC ORP will issue written approval to begin research under separate notification. Written approval to proceed from the USAMRMC ORP is also required for any Research Project Awardee (or lower tier subawards) that will use funds from this award to conduct research involving human subjects. Offerors must allow at least 30 days in their schedule for the ORP review and authorization process.

3.3. Cost Proposal

MTEC will make cost proposal formats available on the Members-Only MTEC website. **The proposal formats provided in the MTEC PPG is mandatory.** The Total Cost by **Clinical Study Cost Element** is required for this solicitation. Refer to the MTEC PPG for additional details.

Costs for the clinical study execution should at a minimum include the following:

1. Clinical study start-up costs and fees
2. Costs per screened volunteer
3. Costs per subject per visit (out-patient volunteer or in-patient volunteer)

Each cost should include direct costs and other necessary components as applicable, for example, fringe, General & Administrative Expense (G&A), Facilities & Administrative (F&A), Other Direct Costs (ODC), etc. Offerors shall provide a breakdown of material and ODC costs as applicable.

3.3.1 Proposal Preparation Cost

The cost of preparing proposals in response to this RPP is not considered a direct charge to any resulting award or any other contract.

3.4. Past Performance Documentation

Offeror shall submit no more than 3 Past Performance References of relevant contracts within the past 3 years for its own performance. The Offeror shall also submit no more than 1 reference for each Subcontractor proposed. The contracts may be past or current as long as the performance did not end more than 3 years prior to the due date for the submission of the proposal, and the contracts may have been with Federal, State and/or City agencies and commercial customers.

(a) Reference Content: It is the Offeror's responsibility to provide valid, current and verifiable references. References must include:

Name of the Organization that will be providing the reference,
Name of the Point-of-Contact(s) (POC),
POC Telephone Number,
POC Email address,
Contract Number,
Total Contract Value,
Period of Performance, and
Scope of Work.

(b) Point-of-Contact(s): The above POCs must be either Government personnel (civil service or military) or employees of private sector clients (such as public or private sector medical facilities) with whom you have provided services. Information provided by or for POCs who work directly for your company, or indirectly (i.e. in a prime or subcontractor relationship), will NOT be considered relevant. Offerors shall ensure that contact information for designated references is accurate and up-to-date.

(c) Information from Other Sources: The Government may consider information obtained through other sources, including but not limited to the Past Performance Information System (PPIRS).

4. **Selection**

The Government will undertake proposal source selection. The proposal source selection will be conducted in accordance with the evaluation factors detailed below. The Government will conduct an evaluation of all qualified proposals. The Source Selection Authority may:

a) *Select the proposal (or some portion of the proposal) for award*

b) *Place the proposal in the Basket if funding currently is unavailable or*

c) *Reject the proposal (will not be placed in the Basket)*

4.1. Proposal Evaluation Process

Qualified applications will be evaluated by a panel of subject matter experts that will make recommendations for funding to the Source Selection Authority appointed by the Commanding General, USAMRMC based on Factors, Sub-factors and criteria described below in the context of the missions of the USAMRMC Dengue Vaccine Program and MTEC.

The RPP review and award process may involve the use of contractors as subject-matter-experts or reviewers; where appropriate, the USG will employ non-disclosure-agreements to protect information contained in the RPP as outlined in Section 1.4.

Evaluation of proposals offered in response to this RPP shall be based on an independent, comprehensive review and assessment against all source selection criteria and evaluation factors, as further described. A rating consistent with these evaluation factors will be derived from the ability of the Offeror to perform the work in accordance with all aspects of requirements outlined in this RPP. The Offeror shall clearly state how it intends to meet the requirements. Mere acknowledgement or restatement of a requirement or task is not acceptable.

Offerors submitting the best value proposals that meet the following Factors and evaluation criteria will be selected for award negotiations:

Factor 1: Technical Approach
Factor 2: Cost-Sharing/ Non-traditional Defense Contractor
Factor 3: Program Management Approach
Factor 4: Past Performance
Factor 5: Cost/Price

Factor Relative Order of Importance: The order of importance for the non-cost/price factors is:

1. Technical Approach
2. Cost Sharing/Non-traditional Defense Contractor
3. Program Management Approach
4. Past Performance

The Technical Approach Factor is more important than the Cost-sharing/Non-traditional Defense Contractor Factor. The Cost-sharing/Non-traditional Defense Contractor Factor is more important than the Program Management Approach Factor. The Program Management Approach Factor is more important than the Past Performance Factor. The Technical Approach, Cost Sharing/Non-traditional Contractor, Program Management and Past Performance Factors, when combined, are significantly more important than the Cost/Price Factor; however, Cost/Price will contribute substantially to the selection decision.

The non-cost/price factors collectively are more important than cost/price. As the collective non-cost factors begin to reach equality in the technical evaluation, cost becomes a more important factor in the trade off analysis.

Table 1 explains the adjectival merit ratings that will be used for the Technical Approach Factor and Program Management Approach Factor.

TABLE 1- GENERAL MERIT RATING ASSESSMENTS	
RATING	**DESCRIPTION**
OUTSTANDING	Proposal meets requirements and indicates an exceptional approach and understanding of the requirements. Strengths far outweigh any weaknesses. Risk of unsuccessful performance is very low.
GOOD	Proposal meets requirements and indicates a thorough approach and understanding of the requirements. Proposal contains strengths which outweigh any weaknesses. Risk of unsuccessful performance is low.
ACCEPTABLE	Proposal meets requirements and indicates an adequate approach and understanding of the requirements. Strengths and weaknesses are offsetting or will have little or no impact on contract performance. Risk of unsuccessful performance is no worse than moderate.
MARGINAL	Proposal does not clearly meet requirements and has not demonstrated an adequate approach and understanding of the requirements. The proposal has one or more weaknesses which are not offset by strengths. Risk of unsuccessful performance is high.
UNACCEPTABLE	Proposal does not meet requirements and contains one or more deficiencies. Proposal is not awardable.

4.1.1. Factor 1. Technical Approach

(1) Ratings. The Technical Approach factor will be evaluated using the merit rating as shown in Table 1.

(2) Factor 1 Evaluation Process.
This factor will be evaluated for the degree to which the technical approach demonstrates a clear working knowledge of what is required to develop the DHIM in order to adequately characterize the challenge strains so that they may be used by the USG, MTEC team partners, and commercial developers to expedite development of dengue countermeasures.

The proposed technical approach will be evaluated on the degree to which it describes in sufficient detail to demonstrate a clear understanding of technical and strategic activities required to develop the DHIM to meet the Government's needs for the following:

Clinical Capabilities
The Technical Evaluation Panel (TEP) will evaluate the degree to which the Offeror demonstrates a clear understanding of the necessary activities required accomplish establishment of regulatory sponsorship for the DHIM characterization studies (DHIM 3, 4, and 2) and the ADVP-005 study; inclusive of the development of CMC IND amendments for the USAMRMC DHIM IND #16332, establishment of necessary CRO activities and other functions required to execute all Sponsor responsibilities, and execution of the DHIM-3, DHIM-2, DHIM-4, and ADVP-005 clinical studies.

The TEP will evaluate the degree to which the Offeror demonstrates a clear understanding of the tasks and activities required to adequately and efficiently conduct clinical characterization of USG dengue challenge strains (DENV 2, 3 and 4) and "field study" ADVP-005 to meet Government goals.

Additional consideration will be given to the degree to which any preliminary existing data supports the proposed objectives. We will assess the validity and suitability of the proposed statistical plan. We will assess whether the proposed efforts will advance the technology maturity level of the DHIM and demonstrate projected performance improvements will be assessed.

The TEP will evaluate the clinical research capabilities communicated in the proposal including both intramural and/or proposed CRO support.

The TEP will evaluate clinical personnel for appropriate and relevant documented education, clinical training, experience, qualifications and availability for the proposed effort. Clinical personnel include the PI, the co- or Associate PIs, lead program managers, key clinical support staff, including Contractors or Sub-Contractors.

Evaluation of personnel will emphasize documented expertise to conduct FDA-sponsored clinical trials as appropriate for the proposed SOW; demonstrated knowledge of DENV pathogenesis; demonstrated knowledge of applicable regulatory guidelines; documented clinical experience with projects of comparable size/scope; experience, training and appropriate certification in infectious diseases; and specific experience as a responsible health-care provider for care of DENV patients.

The TEP will assess the proposal for sufficient clinical expertise and clinical capacity (intramural and/or CRO-based) to enable the Offeror to address the focused execution of clinical characterization of DENV-2, 3, and 4 challenge materials and the ADVP-005 study.

The TEP will evaluate the proposed Clinical Plan for suitability of facilities, equipment, ancillary support staff, medical resources, and the capabilities of site(s) to provide a high quality out-patient clinical site(s) for conducting DHIM protocol(s) in accordance with FDA good clinical practice regulations, as well as access to a supporting, in-patient clinical facility to provide necessary care and monitoring of volunteers with DENV infections and to manage any resultant clinical complications.

The TEP specifically will assess the clinical site capacity relative to conducting trials concurrently for multiple DENV serotypes; geographical location of the site in relation to susceptibility to the dengue vector(s); clinical site experience with conducting FDA-regulated trials; the extent to which the proposal and included Letters of Support make clear the clinical site Institutional Review Board and institutional leadership are supportive of a human disease challenge model involving exposure to live-attenuated virus; the clinical site capacity and infrastructure for supporting the inpatient housing/care of subjects as required by the proposed DHIM protocol(s); clinical support setting experience in the conduct of controlled, human challenge studies with DENV or other live virus materials.

The TEP reserves the right to conduct initial and periodic site visits of facilities to include intramural or CRO out-patient and in-patient clinical sites, as well as other key subcontractor facilities.

Regulatory Affairs and Compliance:
The TEP will evaluate the degree to which the Offeror demonstrates a clear understanding of the necessary regulatory affairs, regulatory submissions, and regulatory compliance tasks and activities required to adequately and efficiently execute sponsor responsibilities, **as the regulatory sponsor**, across the proposed clinical and technical methods to accomplish the SOW and other sections of the RPP. This will include an assessment of project adherence to FDA regulations, other appropriate guidance, and requirements related to development and testing of biologics including, but not limited to, applicable portions of Title 21 of the US Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, the Health Insurance Portability and Accountability Act (HIPPA) of 1996 (Pub.L. 104-191, 110 Stat. 1936, enacted August 21, 1996), and International Conference on Harmonisation Guidelines for Good Clinical Practices (GCPs) (ICH Guidelines for Good Clinical Practice (E6), Published May 9, 1997), ICH M9, and ICH M2.

The overall Regulatory Strategy and Regulatory Plan must be integrated with other program management tools (IMP, IMS, RMP) and will be evaluated under Factor 3.

Manufacturing Capabilities:
The TEP will evaluate the degree to which the Offeror demonstrates a clear understanding of the necessary tasks and activities required to produce and manufacture the DENV-2 live virus challenge material and to ensure production of Government-furnished DENV challenge strains are tested for purity, safety, and potency. We will evaluate methodology to ensure any proposed laboratory and animal testing follows current FDA and ICH guidelines that apply to cell banking and to live-viral vaccine seeds and final products intended for human use.

The TEP will assess proposed DENV challenge strain production methodology proposed for technical feasibility including the following parameters: (1) use of Government-furnished isolates respects all confidentiality of personal identification information; (2) viral passage is conducted in a permissive, qualified cell line; (3) production is conducted under conditions that comply with Phase 1 good manufacturing practice (GMP) and follow FDA recommendations for live vaccine products in testing of vaccine bulk and final container; (4) proposed methodology controls number of passages but retains the ability to scale to desired number of vials (5) all raw materials used in passage have appropriate certificate of analysis and origin for fetal bovine serum and other animal-derived raw materials; (6) final product is freeze-dried in suitable cryopreservative to maintain stability; and (7) plans are described to monitor stability of final product.

4.1.2. Factor 2. Cost Sharing/Non-traditional Defense Contractor

(1) Ratings. The Cost Sharing/Non-traditional Contractor Factor will be evaluated using the merit rating as shown in Table 2:

TABLE 2- COST SHARING/NON-TRADITIONAL CONTRACTOR ASSESSMENTS	
RATING	**DESCRIPTION**
GOOD	Offeror proposing an MTEC research project in which the Offeror provides at least 40% of the total project cost thereby exceeding the minimum acceptable cost share requirements.
ACCEPTABLE	Offeror proposing an MTEC research project meets at least ONE of the following: • Offeror is a Non-traditional Defense Contractor • Offeror's proposal has at least one Non-traditional Defense Contractor participating to a significant extent • Offeror provides at least one third of the total project cost as acceptable cost share
MARGINAL	Offeror proposing an MTEC research project meets at least ONE of the following: • Offeror has at least one Non-traditional Defense Contractor participating, but additional detail is required to determine if non-traditional participation is significant • Offeror has proposed cost share, but additional detail is required to determine if cost share is acceptable
UNACCEPTABLE	Offeror proposing an MTEC research project does **NOT** meet any of the following: • Offeror is a Non-traditional Defense Contractor • Offeror's proposal has at least one Non-traditional • Defense Contractor participating to a significant extent • Offeror provides at least one third of the total project cost as acceptable cost share

(2) Factor 2 Evaluation Process. Each Offeror must have at least one Non-traditional Defense Contractor participating to a significant extent in the performance of an awarded Research Project Award *OR* provide cost share of no less than one third of the value of the Research Project Award awarded to the Member Organization. See RPP for specific details on this evaluation criterion.

Proposals receiving a rating of unacceptable for this Factor will be rejected regardless of the results of any other Selection Factor evaluation. Proposals that receive an overall Technical Approach Factor rating above a "Marginal" but with a Non-traditional Defense Contractor/Cost Sharing rating of "Marginal" may be awarded only if and when non-traditional participation is deemed significant or one third cost share is proposed.

Cost-sharing is a critical element of the DHIM RPP. Proposals will be evaluated based upon the extent to which Offeror proposes acceptable cost-sharing arrangements and in-kind resources to maximize return on USG past and planned investments for the DHIM. In addition to traditional cash and in-kind cost share contributions, Offerors may propose cash generated from projected sales of validated DENV challenge materials during project performance or in-kind exchanges commensurate with the development

investments made by participating team members during project performance for validated DENV challenge materials.

4.1.3. Factor 3. Program Management Approach

(1) Ratings. The Program Management Approach Factor will be evaluated using a subjective adjectival merit rating as described in Table 1.

(2) Assessment of the overall Program Management Approach will include the following areas of evaluation: IMP and IMS, Risk Management Plan (RMP), Regulatory and Quality Management Plans, Teaming Arrangement/Resource Integration, and Commercialization Approach.

Integrated Master Plan and Integrated Master Schedule: We will evaluate the Offeror's draft IMP and IMS and proposed Clinical Study Cost Elements for understanding of all contract terms, conditions and requirements. **The TEP will assess the feasibility and completeness of approach with an emphasis on the efficiency of the Offeror's proposed schedule.**

The TEP will examine the proposed IMP and IMS for critical path, major milestones, activities, duration, Offeror's recognition and evaluation of schedule lead-, lag-, and slack-time, and schedule relationships to manage the required work. The TEP will evaluate plans favorably for concurrent development of DHIM modules for multiple DENV serotypes.

Risk Management Plan: The TEP will evaluate the proposal and draft RMP to determine the Offeror's understanding of an integrated risk management system and their approach for identifying, analyzing, prioritizing, mitigating, and tracking program risks and root cause drivers of program risk.

The TEP will assess risk management of proposed Clinical Plans, especially those risk mitigation steps required for protecting human volunteers. The RMP should be consistent with the proposed Regulatory Plan and the overall IMP and IMS.

Regulatory Plan and Quality Management Plan: The TEP will evaluate the proposed Regulatory Strategy and Regulatory Plan for consistency with the overall draft IMP and IMS. The Regulatory Plan should map specific program milestones, deliverables, resource requirements, and specific testing requirements, viz. standards and guidance, to achieve FDA (or other countries) approval for human use of the DHIM.

The TEP will evaluate the draft Quality Management Plan (QMP) to assess the Offeror's understanding of a quality management system and the approach for maintaining a quality management system compliant with FDA requirements.

Teaming Arrangements/ Resource Integration: The TEP will assess the extent to which the proposed effort manages and captures past and ongoing USG investments by creating or leveraging high-quality teams with experience characterizing DENV-1 (refer to Section 3.2.4 Technical Supplementary Materials for more information of past and ongoing USG efforts).

The TEP will assess the extent to which the technical approach of the proposal effectively incorporates available GFE/GFI challenge materials including: pre-IND meeting summary and clinical results of ongoing DHIM-1 clinical trial NCT02372175; (to the extent these results are made available by the USG during the

award process); government-furnished, vialed cGMP LVHC DENV-1, DENV-3, and DENV-4 challenge material; USAMMDA DM and DSMB resources; and WRAIR clinical screening assays.

The TEP will assess whether the proposal positions the DHIM to be of tangible value to experienced partners interested in using characterized DENV challenge materials for future development of medical products (e.g., vaccines or drug development programs). This includes anticipation of recovering DHIM development costs by in-kind teaming arrangements or partnerships.

The TEP will assess how the proposal addresses teamwork, integration, post-characterization dissemination and management of clinical data, results and samples.

Commercialization Approach: The TEP will evaluate how well the proposal protects and manages collective IP, describes any appropriate IP plan or arrangements among participating teams (if applicable), and addresses the impact of IP issues on DHIM success early in the development process. An effective IP plan will balance protection of assays and methodology against the requirement for dissemination within an MTEC DHIM team of qualified Offerors.

The TEP will evaluate the Commercialization plan for collaborative approaches that communicate realistic understanding of the current and anticipated marketplace; preserve opportunities to share methods and reagents widely across a global consortium of qualified DENV vaccine and therapeutics researchers; develop and protect new IP; and promote greater expansion of use by qualified partners and return on investment of technology developed for the DHIM.

The TEP will assess the Offeror's plan to ensure access to the data and results that will permit other researchers, inside and outside the MTEC DHIM team, to perform valuable exploratory research with unencumbered clinical trial samples.

4.1.4. Factor 4. Past Performance

(1) Ratings. The Past Performance Factor will be evaluated using a subjective adjectival merit rating as described in Table 3.

TABLE 3- PERFORMANCE CONFIDENCE ASSESSMENTS

RATING	DESCRIPTION
Substantial Confidence	Based on the Offeror's recent/relevant performance record, the Government has a high expectation that the Offeror will successfully perform the required effort.
Satisfactory Confidence	Based on the Offeror's recent/relevant performance record, the Government has a reasonable expectation that the Offeror will successfully perform the required effort.
Unknown Confidence (Neutral)	No recent/relevant performance record is available or the Offeror's performance record is so sparse that no meaningful confidence assessment rating can be reasonably assigned.

Limited Confidence	Based on the Offeror's recent/relevant performance record, the Government has a low expectation that the Offeror will successfully perform the required effort.
No Confidence	Based on the Offeror's recent/relevant performance record, the Government has no expectation that the Offeror will be able to successfully perform the required effort.

(2) Factor 4 Evaluation Process. The Government will conduct a Past Performance evaluation of the Offeror's Past Performance as well as that of its subcontractors. Past Performance consists of two aspects for evaluation: past performance relevancy and performance confidence. The Government will evaluate the Offeror's past performance references to determine how relevant a recent effort accomplished by the Offeror is to the requirement to be acquired through this source selection. Common aspects of relevance include similarity of service/support, complexity, magnitude of effort, dollar value, and contract type. Second, the Government will evaluate the Offeror's past performance references to determine the quality of work performed and assess the level of expectation that the Offeror can successfully perform the required effort. Past performance that is found not to be within the past three years or relevant will not be evaluated.

The TEP will also consider past performance and references provided by the Offeror in response to this RPP and the MTEC Member Sheet(s). The TEP also will consider data in past performance repositories or other archival sources, including but not limited to the Past Performance Information Retrieval System (PPIRS), and feedback from members of the evaluation team.

4.1.5. Factor 5. Cost/Price

(1) Ratings. The Cost area will receive a narrative rating to determine whether costs are realistic, reasonable, and complete.

(2) Factor 5 Evaluation Process. The MTEC CM will evaluate the estimated cost proposed by the Offeror for performing all requirements outlined in this RPP. Evaluation will include analysis of the proposed cost together with all supporting information. The Offeror's cost and rationale will be evaluated for realism, reasonableness, and completeness.

The Government Technical Evaluators will assess cost realism as part of the source selection process. If a proposal is selected for award, the MTEC CM will review the original cost proposal and the Offeror's response to a Proposal Update Letter (PUL), if applicable. The MTEC CM will request additional information or clarification as necessary. The MTEC CM will assess the reasonableness and completeness of the cost estimates and then provide a formal assessment to the Government. The Government will review this assessment and make the final determination that the negotiated project value is fair and reasonable.

Proposals will be evaluated using the understanding of cost realism, reasonableness and completeness as outlined below:

(i) Realism. Proposals will be evaluated to determine if Costs are realistic for the clinical work to be performed, reflect a clear understanding of the requirements, and are consistent with the various

elements of the Offeror's schedule proposal that correlate with draft IMP, IMS, SOW, and Clinical Study Cost Element proposed.

Estimates are "realistic" when they are neither excessive nor insufficient for the effort to be accomplished. Estimates must also be realistic for each task of the proposed project when compared to the total proposed cost. For more information on cost realism, please refer to the MTEC PPG.

The MTEC CM will make a determination by directly comparing proposed costs with comparable current and historical data, evaluator experience, available estimates, etc. Proposed estimates will be compared with the corresponding technical proposals for consistency.

(ii) Reasonableness. The Offeror's cost proposal will be evaluated to determine if it is reasonable. For a price to be reasonable, it must represent a price to the government that a prudent person would pay in the conduct of competitive business. Normally, price reasonableness is established through cost and price analysis.

To be considered reasonable, the Offeror's cost estimate should be developed from applicable historic cost data. The Offeror should show that sound, rational judgment was used in deriving and applying cost methodologies. Appropriate narrative explanation and justification should be provided for critical cost elements. The overall estimate should be presented in a coherent, organized and systematic manner.

Costs provided shall be clearly attributable to activities or materials as described by the Offeror in the IMP required in Section 3.1. Costs should be broken down the Cost Proposal Formats and Clinical Study Cost Elements as shown in the mandatory Cost Proposal Formats which are located on the Members-Only MTEC website.

(iii) Completeness. The MTEC CM will evaluate whether the proposal clearly and thoroughly documents the rationale supporting the proposed cost and is compliant with the requirements of the solicitation.

The proposal should clearly and thoroughly document the cost/price information supporting the proposed cost in sufficient detail and depth. The MTEC CM will evaluate whether the Offeror's cost proposal is complete with respect to the work proposed. The MTEC CM will consider substantiation of proposed cost (i.e., supporting data and estimating rationale) for all elements.

Rate and pricing information is required to properly perform the cost analysis of the proposal. If the Offeror is unwilling to provide this information in a timely manner, its proposal will be lacking information that is required to properly evaluate the proposal and the proposal cannot be selected for award.

4.2. Best Value

The Government will conduct the source selection and MTEC CM will award the projects in Best Value sequence. If applicable, the Government will invoke a best value process to evaluate the most advantageous offer by considering and comparing factors in addition to cost or price. Based on the results of the Technical Approach Evaluation, the Government reserves the right to negotiate and request changes to any or all parts of the SOW. Offeror's will have the opportunity to concur with the requested changes and revise cost proposals as necessary.

Definition of General Terms Used in Evaluations:

Strength - An aspect of an Offeror's proposal that has merit or exceeds specified performance or capability requirements in a way that will be advantageous to the Government during award performance.

Weakness - A flaw in the proposal that increases the risk of unsuccessful award performance.

Significant Strength - An aspect of an Offeror's proposal that has appreciable merit or appreciably exceeds specified performance or capability requirements in a way that will be appreciably advantageous to the Government during award performance.

Significant Weakness - A flaw that appreciably increases the risk of unsuccessful award performance.

Deficiency - A material failure of a proposal to meet a Government requirement or a combination of weaknesses in a proposal that increases the risk of unsuccessful award performance to an unacceptable level.

5. ***Points-of-Contact***

Questions concerning contractual, cost or pricing related to this RPP should be directed to the MTEC Contracts Manager, Lisa Fisher at Advanced Technology International via email to Mtec-contracts@ati.org.

Technical related questions should be directed to the MTEC Program Manager, Polly Graham at Advanced Technology International via email at mtec-sc@mtec-sc.org.

Once an Offeror has submitted a proposal, neither the Government nor the MTEC CM will discuss evaluation/proposal status until the source selection process is complete.

6. **Acronyms/Abbreviations**

ATI	Advanced Technology International
ADVP	Alternate Dengue Vaccine Program
CDMS	Clinical Data Management System
CFR	U.S. Code of Federal Regulations
cGMP	Current Good Manufacturing Processes
CM	Consortium Manager
CMC	Chemistry, Manufacturing, and Controls
CRO	Contract Research Organization
DENV	Dengue virus
DHIM	Dengue human infection model
DHIM-x	USAMRMC code for DHIM clinical trials; x corresponds to DENV serotype(s)
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FAQ	Frequently Asked Questions
F&A	Facilities and Administrative Costs
FDA	US Food and Drug Administration
G&A	General and Administrative Expenses
GFE/GFI	Government Furnished Equipment/Government Furnished Information
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Integrated Master Plan
IMS	Integrated Master Schedule
IND	Investigational New Drug
IP	Intellectual Property (e.g., patents, copyrights, licensing, etc.)
LOA	Letter of Authorization; a formal and specific direction to the U.S. FDA that permits entities to cross-reference certain components of an ongoing FDA Investigational New Drug Application
LVHC	Live Virus Human Challenge
ODC	Other Direct Charges
ORP	Office of Research Protections, USAMRMC
OTA	Other Transaction Authority, a form of government contracting **authority** to enter into **transactions other** than traditional contract agreements
PCR	Polymerase Chain Reaction
POC	Point-of-Contact
PUL	Proposal Update Letter
QMP	Quality Management Plan
RMP	Risk Management Plan
SIV	site-initiation visits
SOW	Statement of Work
TEP	Technical Evaluation Panel
USAMMDA	U.S. Army Medical Materiel Development Activity
USAMRMC	U.S. Army Medical Research and Materiel Command
USG	U.S. Government
WRAIR	Walter Reed Army Institute of Research