DARPA-PA-26-09
Resuscitation and Prevention of Ischemia-Induced Dysfunction (RAPIID)

Task Area-3: Regulatory Advancement and Program Infrastructure

Frequently Asked Questions

Version 1
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Clarifications

- DARPA's intent across all clinical and regulatory milestones is to prioritize the most efficient, FDA-aligned pathway to clinical adoption, rather than dictating rigid procedural mechanics.
- The Food & Drug Administration (FDA) is an independent Government agency that is not a participant in the RAPIID program. DARPA will defer to FDA on regulatory matters as this is the mandate for their Agency.
- We use Arabic numerals (Phase 1 and Phase 2) for the phases of the RAPIID program and Roman numerals (Phase I and II) when discussing clinical trial phases.
- Technology Readiness Levels (TRLs) relevant to the RAPIID program are defined here:
  - Link to Integrated Technology Readiness Levels For Medical Countermeasure Products (Drugs and Biologics)
  - Link to TECHNOLOGY READINESS LEVELS FOR MEDICAL COUNTERMEASURE PRODUCTS (DIAGNOSTICS AND MEDICAL DEVICES)

Administrative and Financial Questions

General Proposal & Submission Information

1. **Q:** Page 28 of DARPA-PA-26-09 states the requirements for submissions to include the Common Disclosure Forms for the Biographical Sketch and Current and Pending (Other) Support. Which agency format should be used - NIH, NSF, DOE, NASA, other?
   A: Information about Key Personnel may be presented in the proposer's preferred format as long as it conforms to the formatting requirements listed in the solicitation for the proposal. The Team Member Identification is not part of the page limit.
2. **Q:** Are the Common Disclosure Forms to be submitted as part of the zip archive with Attachments A-F, or separately?
   A: All attachments need to be submitted as a single zip archive to BAAT.

Contracting, Budget, & Milestones

3. **Q:** Page 23 of DARPA-PA-26-09 has the following guidance for Attachment B: "Cost Summary: Provide total effort cost for Phase 1 of TA-3 and a summary of the major cost items." Guidance within Attachment B says "The Cost Proposal must address both RAPIID Phase 1 (Base) and Phase 2 (Option)". Which guidance should be followed?
   A: Please follow the guidance in Attachment B.
4. **Q:** For schedule and budgeting purposes, could DARPA clarify the number of products from TA1 and TA2 expected to advance to TA3 preclinical testing and clinical testing?
   A: For the purposes of budgeting and generating a budget, please use a total of 10 different components for RAPIID Phase 1 and 3-5 different components (at least 1 each of an oxygen carrier, platelet/platelet-like particle, and plasma) for RAPIID Phase 2. The exact number of TA1 and TA2 products is currently unknown and is subject to change. Using this estimated number of products should not be construed as a guaranteed or anticipated number of products that will be made under DARPA-PS-26-124.

5. **Q:** The proposed schedule includes completion of IND-enabling studies, FDA authorization, IRB review, OHRO review, and initiation of a Phase I clinical trial within a compressed timeline. Could DARPA clarify whether these milestones assume standard FDA and human subjects review timelines, or whether milestone adjustments would be considered if regulatory review durations extend beyond performer control?
   A: Please communicate early and often with DARPA should delays arise. DARPA will work with potential performers to address any potential contract modifications that need to be made.
6. **Q:** If FDA requires modification or additional work by TA-1 or TA-2 performers, or protocol changes by TA-3 performers, will DARPA consider milestones missed, or will schedule be adjusted accordingly?
   A: Please communicate early and often with DARPA should delays arise. DARPA will work with potential performers to address any potential contract modifications that need to be made.
7. **Q:** Many TA-3 milestones depend upon timely delivery of products and devices from TA-1 and TA-2 performers. Could DARPA clarify how milestone schedules and associated payments would be handled if upstream technical delays occur outside the control of the TA-3 performer?
   A: Please communicate early and often with DARPA should delays arise. DARPA will work with potential performers to address any potential contract modifications that need to be made.

Engagement with DARPA & Interactions Between Performers

8. **Q:** Will any type of agreements between TA performers be required by DARPA? If performing organizations require agreements (e.g., non-disclosure, data use, material transfer), will they have the ability to develop and implement such agreements with other TA performers independent of DARPA, or will the government require review?
   A: See Section 1.8 of the Program Announcement and Attachment D for information on agreements between performers.
9. **Q:** The solicitation appropriately emphasizes organizational independence. Could DARPA clarify whether prior academic collaborations, multicenter clinical trial participation, publications, or federally funded research involving potential TA-1 or TA-2 performers would constitute a conflict of interest in the absence of financial, commercial, or advisory relationships?
   A: See Section 2.6.4 of the Program Announcement for further details and examples.
10. **Q:** The solicitation emphasizes in-house CRO/ARO capabilities while also permitting tightly managed partnerships for certain activities. Could DARPA clarify which capabilities are expected to reside directly within the prime organization versus those that may be performed through subawardees, academic partners, or qualified contract research organizations?
    A: See Section 2.5 of the Program Announcement.

Security

11. **Q:** Storing and analysis of PHI data does not typically require CUI. Will all information and data pertaining to this award require CUI marking and commensurate information security?
    A: Information security and marking must follow DoD regulation. Please see the CUI guide attached to the Program Announcement for information about what constitutes CUI.

Technical Scope & Task Areas Questions

Regulatory & FDA Strategy

12. **Q:** FDA often requires GLP studies in two species to support IND applications. Does DARPA anticipate GLP studies in a second species will be required? Has FDA provided feedback on whether in vitro plus large animal testing is sufficient?
    A: The FDA is an independent Government agency that is not a participant in the RAPIID program. DARPA will defer to FDA on regulatory matters as this is the mandate for their Agency. Early discussions with FDA (eg, pre-IND meetings) will be important to confirm requirements.
13. **Q:** Have TA-1 and/or TA-2 performers initiated discussions (i.e., pre-sub) with FDA to clarify model requirements? If pre-subs have occurred, will DARPA provide this information to TA-3 performers?
    A: At this time, performers for TA-1/2 have not yet been selected so status of discussions is unknown. However, DARPA anticipates this information could be requested from TA-1/2 performers under the Associate Performer Agreement.
14. **Q:** FDA typically requires review of Phase I data in combination with review of Phase II trial design prior to safe to proceed determination is received for Phase II. Will there be coordination between government agencies to facilitate real-time/seamless review to meet the schedule of milestones?
    A: DARPA anticipates leveraging existing workflows between DoD and FDA as relevant and possible.
15. **Q:** The regulatory strategy may require all components to have independent FDA approval prior to submitting regulatory package for a combination/system. Could DARPA clarify how this would be addressed in the provided schedule of milestones?
    A: The goal for the RAPIID program is to get individual components to at least EUA in FY 2029 while also testing the use of the individual components in combination so military health care providers have information regarding their use in combination and can make informed practice of medicine decisions when they have access to these products.
16. **Q:** Will the clinical trial endpoint/primary outcome be guided by FDA recommendations (ie oxygen delivery, hemostasis, or volume restoration) and aimed at demonstrating efficacy for intended indication/labeling? Will endpoints be guided by FDA recommendations?
    A: The Food & Drug Administration (FDA) is an independent Government agency that is not a participant in the RAPIID program. DARPA will defer to FDA on regulatory matters as this is the mandate for their Agency.
17. **Q:** The approval of CPGs will likely require at least an Emergency Use Authorization from FDA for battlefield use for novel products and devices. Given the goal of CPG submission by month 36, what is the expected timeline for EUA after phase II trial completion?
    A: The goal for the RAPIID program is to have individual component EUAs submitted in month 36. The CPGs are being drafted and finalized in parallel with this work to minimize lag time until fielding in the event of an EUA being granted.
18. **Q:** The Preclinical Evaluation description in the TA-3 solicitation discusses combination testing only, whereas Table 1 indicates TA-1, TA-2, and TA-3 performers will be involved in individual product testing and regulatory package submission. Additionally, TA-3 is indicated as the performer for system preclinical testing and regulatory engagement. Could DARPA clarify if the intent of a

combination/system is an integrated product (i.e. one product that contains multiple components with one label/indication), or if the intent is a family of products with individual FDA approvals and TA-3 performers examine improvements in outcomes when multiple products are used?
A: The goal for the RAPIID program is to get individual components to at least EUA in FY 2029 while also testing the use of the individual components in combination so military health care providers have information regarding their use in combination and can make informed practice of medicine decisions when they have access to these products. Decisions regarding packaging and labeling of the blood analog system have not been made at this time.

19. **Q:** The Technical Management Plan requests information on "system-level clinical trials". Could DARPA elaborate on the intended meaning of "system-level clinical trials"?
A: Given the rapid execution timelines required by the RAPIID program, traditional clinical trial design/strategies are unlikely to be a suitable approach to clinical evaluation. The term "system-level clinical trials" is meant to convey that potential performers could consider clinical design/strategies beyond the traditional approach. Potential performers should provide rationale for the design they have selected.
20. **Q:** Will study design for preclinical and clinical phases be investigator initiated in collaboration with TA-1/TA-2 performers, or does DARPA intent to provide direct government instruction?
A: Study designs for preclinical and clinical phases should be performer-led to maximize execution velocity through the FDA regulatory pathway. While DARPA will leverage existing DoW-FDA workflows, DARPA does not intend to provide top-down government instruction.

Cross-TA Dependencies & Program Integration

21. **Q:** The solicitation describes TA-3 responsibilities for regulatory advancement and transition activities while TA-4 focuses on commercialization and sustainment. Could DARPA clarify the intended division of responsibilities between these task areas, particularly with respect to manufacturing readiness, market analysis, transition planning, and commercialization strategy?
A: TA-3 is responsible for manufacturing readiness only as far as it pertains to procuring product needed for evaluations. Landscape assessments of manufacturing readiness, market analysis, transition planning, and commercialization strategy and providing recommendations to TA-1/2 performers is out of scope for TA-3 and will be handled by TA-4 performers.
22. **Q:** The Safety and Efficacy Report – Combination Blood Analog has a milestone at month 6 and month 9 with slight difference in performance criteria. Are TA-1 performers expected to make changes to their product between months 6 and 9 that would change performance? If so, how will this be accounted for in the timeline?
A: TA-1 performers should have their formulation design locked no later than Month 6. The increased stringency in performance criteria at Month 9 should allow for sufficient time to do combination testing for any products which do not design lock until that time.
23. **Q:** Will DARPA provide guidance on type of in vitro testing required, or is this up to the TA-3 performing organization and dependent on product mechanism of action?
A: In vitro work with combinations of products will be performed by a Government IV&V partner. However, if potential performers think additional *in vitro* studies are warranted, they should propose and scientifically justify their inclusion.

TRL/MRL & Material Readiness

24. **Q:** Could DARPA clarify their definition of “design-locked” at Month 7? Is this inclusive of final formulation, dose, packaging, manufacturing?
    A: Design lock refers to the formulation of the components in TA-1.
25. **Q:** What minimum data packages will TA-1 and TA-2 performers be expected to provide (e.g., prior animal data, safety data, manufacturing information, release testing, stability data)?
    A: TA-1/2 performers have not yet been identified and may have products at different TRL/MRLs. As such a minimum data package cannot be defined at this time.
26. **Q:** Will clinical-grade material be available before TA-3 period of performance start, or will this material be manufactured during the first 12 months?
    A: TA-1 performers have not yet been identified and may have products at different TRL/MRLs. As such availability of clinical-grade material cannot be defined at this time.

Preclinical

27. **Q:** Other than large animal GLP models, does DARPA have additional requirements for model type such as survivable vice lethal hemorrhage, duration of survival, etc?
    A: Potential performers should recommend what model they think is most appropriate and provide supporting information as to why this is an appropriate model.
28. **Q:** The Technical Management Proposal Template section 2 specifies “in vitro, small animal, and large animal models”, whereas the TA3 solicitation only discusses large animal GLP models. Can DARPA clarify if TA3 performers are expected to conduct preclinical experiments in small animal models?
    A: Potential performers should include any/all studies they think are necessary to achieve the metrics outlined in Section 1.6.2/Table 3 and Section 1.6.3/Table 4.
29. **Q:** The solicitation states that proposers should demonstrate GLP-compliant large animal capabilities while also allowing an expedited pathway to GLP compliance. Could DARPA clarify whether existing GLP capability is required at the time of award, or whether established partnerships with GLP-qualified CROs or implementation of GLP capability during Phase 1 are considered acceptable?
    A: GLP capability does not need to exist at time of award. Potential performers should clearly demonstrate how they intend to provide this capability in their proposals whether that is through partnerships, qualification, or another approach.
30. **Q:** Please clarify which endpoints determine the 20% and 10% non-inferiority margins: survival, lactate clearance, oxygen delivery, hemodynamics, coagulation, bleeding, organ injury, or a composite endpoint?
    A: Non-inferiority margins must be determined by clinically relevant endpoints that are directly tied to safety, efficacy, and the expected requirements for FDA licensing. While performers must scientifically justify their chosen endpoints, these metrics should be heavily informed by historical precedents and established product standards.
31. **Q:** Several milestones require demonstration of non-inferiority to "stored whole blood." Could DARPA clarify the intended comparator, including storage duration, anticoagulant/preservative solution, leukoreduction status, pathogen reduction status (if applicable), and whether the

comparator should reflect current military low-titer group O whole blood practice or civilian blood banking standards?
A: DARPA does not / will not prescribe a single, rigid specification for the "stored whole blood" comparator. Performers should define and scientifically justify their selected comparator profile, ideally testing across a range of storage durations to demonstrate performance range of the whole blood analog.

32. **Q:** The solicitation requires evaluation of compatibility with commonly deployed trauma countermeasures. Could DARPA clarify whether DARPA intends to provide a required list of medications and products (e.g., tranexamic acid, calcium, plasma, vasopressors, ketamine, crystalloids), or whether proposers should develop and justify the interaction testing panel?
A: Potential performers should define and scientifically justify the products they intend to include in their interaction testing panel.
33. **Q:** Does DARPA anticipate a single dose equivalent of TA-1 products be administered and evaluated, or is repeat dosing anticipated?
A: Currently, serial and repeat dosing of Technical Area 1 (TA-1) products is anticipated in preclinical testing. Potential performers should evaluate dosing regimens to determine the safety and therapeutic efficacy of the analog.

Clinical

34. **Q:** Given the requirement for combination testing, is there any stipulation or precondition on trial design? Can trials run concurrently with shared controls?
A: Potential performers should propose the clinical trial plan they believe will meet the metrics, milestones, and timeline outlined in the Program Announcement and provide rationale for the design they have selected.
35. **Q:** Does DARPA have a specific comparator in mind (e.g., only whole blood, component therapy [1:1:1])?
A: Ideally, individual components will be compared to the most relevant matching component from component therapy with the combinations being compared to stored whole blood. However, DARPA will defer to FDA's authority regarding clinical trial design.
36. **Q:** Could DARPA clarify the intended use case? For example, bridge to transfusion from point of injury to higher level of care, adjunct during massive transfusion, or full whole blood substitute.
A: The intended use for the whole blood analog is to be a resuscitation product to treat active bleeding due to traumatic injury when whole blood is unavailable. Because whole blood may not be available for a variety of reasons (logistics, scarcity, etc) the use may cover multiple clinical uses.
37. **Q:** The Phase 2 milestones require initiation of a Phase I clinical trial (Month 14), followed by demonstration of non-inferiority to stored whole blood safety during the Phase I study (Month 20). Phase I first-in-human trials typically occur in health volunteers; Phase I or II "first in patient" trials typically require non-trauma populations to allow for prospective informed consent prior to proposing EFIC studies in trauma populations. If this typical progression is required by FDA, could DARPA clarify how this will align to the solicitation's intent and if the schedule and milestones will be adjusted accordingly?

A: Potential performers should define and scientifically justify their clinical trial design, including appropriate trial populations. To maximize efficiency, performers are highly encouraged to propose innovative, adaptive, or seamless trial designs appropriate for synthetic biology products (e.g. combined phases and/or platform designs) to accelerate clinical evaluations. DARPA recognizes that FDA alignment is necessary to define the appropriate clinical progression for innovative products.

38. **Q:** Section 1.3 states that TA-3 will design and conduct Phase I and Phase II clinical trials, "which may include EFIC." Since EFIC under 21 CFR 50.24 is generally applicable to emergency research in subjects unable to provide prospective informed consent, while Phase I studies are commonly conducted in healthy volunteers or prospectively consented patients, could DARPA clarify whether EFIC is anticipated only for later-stage trauma studies (e.g., Phase II or first-in-patient emergency studies), or whether proposers should plan for the possibility of EFIC during Phase I clinical development?
    A: DARPA acknowledges that Phase I First-In-Human trials may utilize consented healthy volunteers or stable patient populations, subject to FDA review. EFIC protocols under 21 CFR 50.24 are not anticipated or required for Phase I development. However, EFIC may be necessary for Phase II clinical development. Potential performers should outline a trial design that is efficient, scientifically justified, makes sense for the technology, and demonstrates a seamless transition from Phase I to Phase II without delaying the overarching program timeline.
39. **Q:** The solicitation references demonstrating non-inferiority within specified margins but does not define the primary endpoints for comparison. Could DARPA clarify whether non-inferiority should be based on survival, oxygen delivery, coagulation function, lactate clearance, organ injury, bleeding, transfusion requirements, or another predefined primary endpoint? Is there a hierarchy of endpoints DARPA would like to see examined?
    A: Proposers are expected to leverage their regulatory expertise to define what an acceptable FDA clinical endpoint(s) to demonstrate safety and efficacy for the intended use of the blood analog/components. Rather than DARPA dictating these metrics, the performer must propose and justify the specific clinical endpoints that are most appropriate for the investigational product(s). DARPA anticipates working iteratively with the selected performer to refine this strategy into a mutually agreed-upon approach that aligns with FDA feedback and TA-1/2 performers as the program progresses.
40. **Q:** The solicitation indicates that TA-1 performers prepare IND/IDE submissions for individual products while TA-3 serves as Sponsor of Record for regulatory activities. Could DARPA clarify whether TA-3 is expected to serve as Sponsor of Record only for integrated blood analog system clinical trials, or also for individual TA-1 component clinical studies?
    A: TA-3 is expected to serve as Sponsor of Record for clinical trials funded under the RAPIID program involving both individual TA-1 components and integrated combinations, as appropriate. DARPA will not require TA-1 or TA-2 performers to transfer ownership of any pre-existing INDs or IDEs to TA-3. Furthermore, TA-1/2 performers are not required to disclose proprietary information to TA-3 regarding independent, non-program-funded clinical trials. The final regulatory structure may vary based on product maturity and FDA feedback, but DARPA intends to facilitate speed, flexibility, and unified accountability.