Early Detection Research Network (EDRN)'s Clinical Validation Centers (CVCs): Frequently Asked Questions (FAQs) on the CVC FOA RFA-CA-21-033 (U01 – Clinical Trial Optional)

To potential applicants: We appreciate your interest in the EDRN CVC FOA and we hope that you and your team will choose to submit an application. To maximize your chances of success, we have provided answers to the questions that were submitted to the NCI Program via email and during the July 12 pre-application webinar, assuming that these questions could be of interest to many additional potential applicants. For additional questions or clarifications, we encourage you to contact the NCI scientific staff mentioned in the CVC FOA.

Q.1: Do you need all 3 phases from a single proposal? Or one of the 3 phases sufficient for one UO1 app?

A.1: Proposing one biomarker validation study at any of the EDRN-defined phases 2, 3 or 4 will be sufficient for an application in response to the CVC FOA. However, applicants must describe in detail their expertise and ability for conducting Phase 4 biomarker utility trials. The EDRN intends to conduct one or two biomarker utility trials, which will be designed post-award under the guidance and approval of the EDRN Steering Committee available. Applicants responding to the CVC FOA should express their interest in participating in such trials and list resources available to support these trials.

Q.2: Does validation require CLIA lab?

A.2: Although a proposed biomarker clinical validation does not require a CLIA lab, it is desirable that the biomarker assay included in a proposed advanced phase 2, 3 or 4 validation study has been optimized and standardized into a clinical grade assay in collaboration with a CLIA-certified lab.

Q.3: Is there a minimum number of projects that should be included in CVC applications?

A.3: No, there isn't a required number of projects that have to be included in a CVC application.

Q.4: Is the page limit 30 regardless of number of projects proposed?

A.4: Yes, applicants must adhere to the 30-page page limit for describing the Research Strategy in a CVC application as indicated in the FOA.

Q.5: Is Previous Accomplishments section sub-section B of the Research Strategy required for new applications?

A.5: While all applications in response to the CVC FOA must include preliminary data in support of the proposed biomarker research and clinical validation, Previous Accomplishments are a requirement for incumbent applicants only.

Q.6: How many Validation centers will be awarded? Are there guidelines for the minimum/maximum number of biomarkers proposed to be tested and the number of cancers types included in the proposal?

A.6: NCI intends to commit up to $10.5M in FY2022 and $15M per year in FY2023-FY2026 to fund meritorious CVC applications at a direct cost per award not to exceed $550K in FY2022 and $785K per year in FY2023-FY2026.

Q.7: Does the direct costs cap exclude indirects from consortia sites?

A.7: It is standard NIH policy that third party Facilities & Administrative (F&A) cost is not included in any Direct Cost caps indicated in a FOA. If an application submitted in response to the EDRN CVC FOA (this also applies for the BCC and DMCC FOAs) has subawards, then the F&A/Indirect costs on the subaward(s) are not included in the calculation of the overall Direct Cost of the proposed studies.

Q.8: May I ask if we only collect specimens for validation research and not initiate clinical trials, is this case Okay?

A.7: Proposal of prospective collection of specimens is allowed only in conjunction with a proposed biomarker validation study and as long as the collection will allow the completion of the proposed validation study within the time frame of the CVC award.

Q.9: Are biomarkers proposed to be tested need to be commercially available?

A.9: Proposed biomarker validation studies may include previously identified biomarkers for which assays are commercially available in cases where the named biomarker has not been validated for the organ site(s) of focus included in the validation study or in cases where the named biomarker has not been previously evaluated according to the EDRN-defined Phases 2, 3 or 4 and in compliance with the principles of the PRoBE or a similar study design.

Q.10: when will special study review section participants be published?

A.10: It is standard NIH policy that the Reviewers' Roster is made publicly available 30 days prior to the scheduled date of the Special Emphasis Panel that will be convened to review applications submitted in response to the EDRN CVC (as well as the BCC and DMCC) FOAs.

Q.11: The FOA states that one area to address is "Facilitate the development of high-throughput, sensitive assay methods to identify, verify and validate biomarkers that are useful in assessment of risk, detection, diagnosis and prognosis of early stage cancers or their lethal precursors." Does this mean studies could focus on markers of recurrence/prognosis for say stage I and II cancers?

A.11: Applications focused on the development and validation of prognostic biomarkers, biomarkers for prediction/ early detection of cancer recurrence, and biomarkers for distinguishing indolent from aggressive precancers or early stage cancers are appropriate for the EDRN CVC FOA.

Q.12: Is it compliant to collect not just samples, but also a "virtual repository" of histology images from samples being collected on the trials?

A.12: Yes, it is appropriate to collect in a virtual repository histology and other images from samples being collected in clinical trials.

Q.13: As part of CVC, can we propose a project to validate FDA approved markers in different race/ethnic populations?

A.13: It is appropriate to propose the validation of FDA approved markers in different race/ethnic populations if such biomarkers have not been tested in such race/ethnic groups and if there is preliminary evidence that the performance of the proposed biomarkers is significantly different in these race/ethnic populations.

Q.14: Are the clinical trials proposed for this RFA limited to phase 3 or 4?

A.14: The CVC FOA will support EDRN-defined Phase 2, Phase 3 and Phase 4 biomarker clinical validation studies.

Q.15: The FOA uses both cost effectiveness and clinical utility somewhat interchangeably what do you mean or can you give us more detail how these are being defined by the EDRN?

A.15: An EDRN-defined Phase 4 validation study (or clinical utility trial) would entail the prospective testing of a validated biomarker to determine the extent and characteristics of disease detected by the biomarker test, as well as the operating characteristics of the biomarker test in a relevant population by determining the detection rate and the false referral rate. Please see publications: Margaret Sullivan

Pepe et al. *J Natl Cancer Inst*, Vol. 93, No. 14, July 18, 2001 and Margaret Sullivan Pepe et al. *J Natl Cancer Inst*, Vol.100:1432-1438, 2008.

Q.16: So biomarkers to predict recurrence among early stage resected cancer would be acceptable?

A.16: Please see answer A.11 above.

Q.17: We can prospectively collect many specimens at the pre-cancer to early cancer stage, but there is no consent for genomic data sharing. Would sharing de-identified methylation processed data rather than raw data be allowable?

A.17: The NIH Genomic Data Sharing (GDS) policy will apply if genomic-wide DNA methylation-specific sequencing (DNAmethyl-seq) analysis on more than 100 samples is proposed. The submission of de-identified data is expected. The NIH GDS policy does not expect submission of raw sequence data. Since processed DNAmethyl-seq data is still potentially identifiable, an IRB approval will be required.

Q.18: I am interested in validating optical spectroscopy biomarkers for lung cancer detection. These include, but not limited to tryptophan, collagen, NADH, etc. Using a bronchoscopy device working channel, optical probe can be used to diagnose pre-cancerous lesions with these biomarkers. Is this something EDRN have investigated or have some interest investigating?

A.18: The described studies are appropriate for an application in response to the EDRN CVC FOA. However, it is well known that a large proportion of pre-cancerous lesions are not destined to progress to cancer or life-threatening disease and their detection may further increase the burden of overdiagnosis to public healthcare. Hence, applicants should consider addressing this issue as part of the proposed studies.

Q.19: How about the biomarkers for predicting drug response?

A.19: Applications focused on biomarkers predicting drug response will not be supported by the EDRN CVC or BCC FOAs.

Q.20: Will single-site applications be competitive or is there increased interest in applications that are doing multiple cancer types?

A.20: No selection preference will be given to meritorious applications based solely on whether they are focused on multiple organ sites or on single cancer types.

Q.21: Are comparisons of different technologies for assessing a biomarker appropriate?

A.21: Comparisons of different technologies for assessing a biomarker are appropriate as long as they are within the context of a proposed EDRN-defined phase 2, 3 or 4 clinical validation study.

Q.22: Is there interest in oral cancer CVC?

A.22: Applications proposing a validation study for biomarkers for detection and/or prognosis of early-stage oral cancer are appropriate for the EDRN CVC FOA.

Q.23: Could an academic investigator and a scientist at a company serve as co-PIs on a CVC application?

A.23: Academic and industry investigators can serve as co-PIs on an application to the EDRN FOAs.

For any further questions on the CVC FOA, please contact:

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