Guidance for reporting the Translational Pipeline Stages for proposed BLRD Merit Award Applications.

Introduction

To enhance the real-world impact of preclinical research aimed to improve Veterans healthcare, BLRD Service is instituting a new requirement for applying VA investigators to specify the translational stages of their proposed projects. **Investigators are required to complete and upload an Appendix where they will indicate the Translational Pipeline (TP) Sub-Categories that their proposed Aims will address.** The information requested in the Appendix are not part of the scoring criterion of your proposal but will be used by BLRD for programmatic purposes, including developing new translational resources for VA investigators.

BLRD Purview

BLRD funds preclinical biomedical and behavioral studies of disorders and diseases prevalent in the Veteran population. The BLRD purview includes in vitro and in vivo studies using tissue cultures, animal models or human biological samples, collected using minimally invasive procedures (blood, urine, buccal swabs) or from tissues acquired without direct contact with subjects (e.g., from tissue banks or pathology material). BLRD will fund discovery research involving -omic data, including related phenotypic data in studies of genetic risk factors, pathophysiological pathways, treatment target identification and biomarker discovery. VA will not fund studies of human fetal tissue. Applications that seek to administer surveys or questionnaires (e.g., new clinical data collection), or perform medical procedures and treatments (including biopsies) or observational studies should be submitted to a Clinical Sciences Research & Development (CSRD) RFA.

BLRD applicants are encouraged to submit innovative and clinically relevant research projects with the potential to significantly advance health care for Veterans. Examples of BLRD's priority research areas include, but are not limited to:

- Posttraumatic stress disorder
- Suicide prevention research (with emphasis on biological markers)
- Modifiable risk factors (e.g., smoking, substance abuse)
- Military service or deployment-related occupational exposures
- Women Veterans' health
- Genomic and personalized/precision medicine
- Pain and neurological disorders
- Metabolic disorder/diabetes
- Health disparities and conditions that impact underserved Veterans, including but not limited to racial and ethnic minority Veterans, Veterans with disabilities and LGBTQ+ Veterans

Information on ORD's Translational Pipeline Stages

In order for VA investigators to identify the Translational Pipeline (TP) stages of their proposed projects, BLRD has modified the TP stages of T0 to T4 proposed by the Institute of Medicine and NIH's Clinical Translational Science Award program [Surkis et. al., J Transl Med (2016) 14:235]. The preclinical biomedical research supported by the BLRD Service is represented in the stage T0. Thus, the T0 stage covers the broad scope of research from initial understanding of the disease biology to moving a therapy towards evaluation in the humans.

Since it is unlikely that a 4-year Merit Award can move the initial discovery to the regulatory submission stage for their use in human studies, the T0 stage is further subdivided into 5 TP substages to represent research studies that must be performed to move the project along the translational pathway. These substages are further sub-categorized into 14 TP Sub-Categories described in **Table 1** to indicate the types of studies that might be appropriate for each sub-category. We consider that studies in each of

these TP sub-categories can potentially be accomplished within the duration of one or two funded Merit Awards.

Table 1

VA-ORD Translational Pipeline (TP) Stages*		
TP Stages	**TP Substages**	**TP Substages Sub-Categories & Definition**
T0: Basic Biomedical Research	**T0-1: Disease Biology / pathology (Foundational Studies)**	**T0-1A: Studying disease/condition to understand pathology and disease progression; biological, social and behavioral mechanisms underlying health or disease.**
		T0-1B: Developing / evaluating novel approach/strategy to address unmet clinical need.
		T0-1C: Focused characterization of select pathway, metabolomic-, proteomic-, genomic - data & epidemiologic studies using existing large data sets etc. to identify key approach or target.
	T0-2: Target Identification, Evaluation & Efficacy (Proof-of-Concept Studies)	**T0-2A: Confirming role of target or approach in disease/condition**
		T0-2B: Developing therapeutic approaches based on target/ concept to improve a clinical condition; can include initial studies on lead molecule screening, developing prototype and assessments.
		T0-2C: Proof-of-concept studies in animals to demonstrate feasibility of approach or therapy to address unmet clinical need.
	T0-3: Validation to de-risk clinical development	**T0-3A: Studies in additional disease model(s) to de-risk potential human translational concerns.**
		T0-3B: Validation of biomarkers, diagnostics etc. in different (gender, race etc.) populations to determine target group.
		T0-3C: De-risking known FDA-recognized issues with the translational approach.
	T0-4: IND/IDE Enabling and Developmental Studies Stage I (Generate Data for FDA INTERACT Meeting)	**T0-4A: Lead/device isolation /development, optimization and selection.**
		T0-4B: Lead candidate or device selection & profiling manufacturing, stability, solubility, immunogenicity, PK/PD, ADME, preliminary GLP-Toxicology.
		T0-4C: Pre-IND/IDE discussion with FDA. Develop plans for biomarkers, immunogenicity assays, etc. Develop plans for GMP manufacturing, and for clinical evaluation.
	T0-5: IND/IDE-Enabling Studies Stage II	**T0-5A: GLP-Tox, determine and convert safe animal dose to starting dose for FIH, GMP manufacturing, drug stability, validating biomarkers and assays for clinical trial, etc.**
		T0-5B: IND/IDE submission, any additional studies required by FDA for regulatory approval
T1: Translation to Humans	**T1: Phase I safety trials**	**T1: First in human, dose escalation safety studies to determine recommended starting dose. Focuses on new methods of diagnosis, treatment, and prevention in a controlled environment.**
T2: Translation to Patients	**T2 : Human efficacy; Phase II and Phase III trials**	**T2-A: Phase II trial; Determine safety and efficacy of therapy in patients (dose response).**
		T2-B: Phase III larger clinical trials to establish efficacy & optimal use in humans.
T3: Translation to Practice	**T3: Translation to clinical Practice**	**T3: Phase IV trials, Comparative effectiveness trials, pragmatic clinical trials, community based participatory research, dissemination and implementation research, etc. Health services research. Meta-analyses, and systematic reviews involving interventions. Development and implementation of evidenced-based guidelines, policies, and best practices.**
T4: Translation to Communities	**T4: Implementation studies**	**T4: Implementation, population monitoring of morbidity, mortality, health impact, Life cycle Management, Durability of Intervention. Wider dissemination/implementation of improved practices/interventions. Studies on impacts of policy and/or environmental change. Studies focusing on disease prevention through lifestyle and behavioral modifications.**

*** Modified From: Surkis et al. J Transl Med (2016) 14:235 "Classifying publications from the clinical and translational science award program along the translational research spectrum: a machine learning approach."**

In addition to T0 to T4 Translational Pipeline stages, several other translational schemes have been used by governmental agencies and industry to monitor the translational readiness of projects on the commercialization pathway. The VA Technology Transfer Program (VA-TTP) uses the NIH Centers for Accelerated Innovations (NCAI) Translational Readiness Levels (TRLs) for their evaluation of their BRAVE Funding proposals to support VA owned/co-owned inventions for commercialization success (see **Table 2** and associated links for more details). As the translational products resulting from preclinical research can include drugs, biologics, devices, diagnostics, or software etc., it is difficult to develop a TP sub-category scheme that will encompass all types of translational research projects. The NCAI TRLs that VA-TTP provide three separate TRL stages and associated milestones for Drugs/Biologics, Therapeutic Devices, and Diagnostic (Assays/Tests) projects. The need to have three separate TRL categories and associated milestones emphasizes the specific translational requirements for different therapeutic categories. **Table 2** provides an approximate correlation between the TP Sub-

Categories proposed in **Table 1** with the TRLs that are currently being used by VA-TTP to assist investigators working in one of these three translational areas. Investigators who are unsure about the TP Sub-Categories of their project from the information provided in the **Table 1**, are encouraged to also use the information in **Table 2** and the associated references to identify the TP Subcategory that is appropriate for their projects.

Table 2

ORD Translational Pipeline*		NCAI Technology Readiness Guidelines (TRL)**			
TP Substages	**TP Sub-Categories**	**Drug / Biological**	**Therapeutic Device**	**Diagnostics (Assay/Test)**	**Activities**
T0-1: Disease Biology / pathology	T0-1A:	TRL1	TRL1	TRL1	Review of Scientific Knowledge Base
	T0-1B:	TRL2	TRL2	TRL2	Development of Product Hypothesis
	T0-1C:				
T0-2: Target Identification, Evaluation & Efficacy (Proof-of-Concept Studies)	T0-2A:		TRL3	TRL3	Identification and Characterization of Product Candidate
	T0-2B:	TRL3 & 4			
	T0-2C:				
T0-3: Validation to de-risk clinical development	T0-3A:		TRL4		
	T0-3B:				
	T0-3C:				
T0-4: IND/IDE Enabling and Developmental Studies Stage I (Generate Data for FDA INTERACT Meeting)	T0-4A:				
	T0-4B:		TRL 4 & 5	TRL 4	Optimization and Initial Demonstration of Safety and Efficacy
	T0-4C:				
T0-5: IND/IDE-Enabling Studies Stage II	T0-5A:	TRL4 & 5	TRL6	TRL 5	Advanced Characterization of Product and Initiation of Manufacturing
	T0-5B:	TRL6		TRL6	Regulated Production, Regulatory Submission, and Clinical data
T1: Phase I safety trials	T1:				
T2: Human efficacy; Phase II and Phase III trials	T2-A:	TRL7	TRL7	TRL7	Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)
	T2-B:	TRL8	TRL8		Completion of GMP Validation and Consistency Lot Manufacturing, Clinical Trials Ph3, and FDA Approval or Licensure
T3: Translation to clinical Practice	T3:				Phase IV trials, Comparative effectiveness and pragmatic clinical trials, community based participatory research, etc.
T4: Implementation studies	T4:				Implementation research, population monitoring of morbidity, mortality, health impact, and Life cycle Management, etc.

*** For definitions of TP Substages Sub-Categories please see Table 1.**

**** For definitions of TRL Stages see the VA-TTP BRAVE Funding page for TRL guidelines that is based on the NCAI TRL guidelines.**

Guidance to Complete the Questionnaire in the Appendix

The Appendix requires the investigator to answer three questions:

1) the TP sub-categories of the proposed project;
2) whether the investigator considers that the successful completion of the proposed project will move the project to a different TP sub-category, and;
3) for renewal applications what the TP sub-categories were for the previously funded project.

Investigators are encouraged to review this guidance document and the information included in the RFA. Additionally, an Excel file that combines the information provided in the **Tables 1** and **2**, and the PDF files of the references cited in these **Tables** is included in the Guidance Folder. The information provided in these documents will assist you in identifying the TP Sub-Categories of your project. Additionally, critical evaluation of the objectives of each Aims and the final outcomes of the proposed study, may help you in determining the correct Sub-Category. Please note that the various Specific Aims in a proposal might represent different TP sub-categories, which might also be impacted by the type of research (bench to bedside vs. bedside to bench etc.) being studied.

We expect that this effort will enhance the translational impact of biomedical research on the clinical care of Veterans. Additionally, it will provide the investigators a pathway that they can pursue to move their discoveries to the clinic. Investigators should reach out to their Scientific Program Manager for any assistance required in responding to the questions proposed in the Appendix.