**Supplementary Material 3. Screener Training Documents**

Despite the availability of an NIH-wide definition of translation, there is considerable variation in its application and in the definitions of individual stages of translation across the more than 60 CTSA hubs funded by NCATS. To account for this variation, our team developed training documents for our reviewers prior to the start of data extraction.

**Translational Science at Tufts CTSI**

**Background**

**What is Translational Research?**

As defined by the NIH National Center for Advancing Translational Sciences (NCATS), ***translation*** is “the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and populations – from diagnostics and therapeutics to medical procedures and behavioral interventions.”

Tufts CTSI focuses on *translating research into impact on health*. This means, translational science that:

* connects biomedical, clinical studies, and behavioral observations and interventions to changes in clinical practice, the health of communities, and health policy, with the clear objective of having a positive impact on health, and
* is patient- and population-oriented, so the public gets a significant return on investment.

**Defining Translational Spectrum for Tufts CTSI**

In creating the NIH CTSA program, “clinical and translational science” was advanced by NIH Director Elias Zerhouni to address “translational blocks” or impediments to the translation of basic research into improvements in health.[[1]](#footnote-1) The initial focus was on the translation of bench research into demonstrated effects for patients, “bench-to-bedside” translation. It soon came to include translation from studies of treatments into usual clinical care. These were referred to as the first and second blocks to translational research, “T1” and “T2,” respectively. It also has been appreciated that for maximal impact, these advances needed to be further translated, and “T3,” implementation and dissemination into wide use, and “T4,” translation into impact on the public’s health and public policy, were articulated. It should be noted that for Tufts CTSI, whether early in the translational pathway or later, all translational research must have a clear line of sight to translation into potential impact on health. To ensure that, especially for very early work, we expect investigators, as part of that clear line of sight, to have understanding of the next steps for their work if it is successful.

As defined below, Tufts CTSI also recognizes a critical phase which cycles between “basic” research and early clinical investigation (T1), which we call T**.**5 research. This bidirectional, nonlinear phase incorporates clinical insights and relevant constraints into the pre-clinical studies with the ***explicit, well-defined, and foreseeable*** purpose of delivering effective and impactful healthcare interventions.

Tufts CTSI supports the work of researchers across the full spectrum of T**.**5-T4 translational spectrum that is focused on *developing treatments, improvements in clinical practice, implementation and dissemination of research discoveries, or changes in policy to improve the public’s health.* We prioritize applied research involving people and communities, or materials of human origin (e.g., tissues). Such research includes, but is not limited to, the direct testing and/or evaluation of diagnostics, therapeutics, devices, medical procedures, behavioral and other preventive interventions, and the dissemination and implementation of interventions to ensure they are effectively delivered. While studies involving human subjects help to validate proximity to clinical impact, we also support some translational studies using model systems such as animal models, computer simulations and other pre-human representations, where the application of such systems is well-justified and serves to accelerate, improve, or otherwise de-risk the translational pipeline. Translational research can also encompass research on naturally occurring diseases shared by animals and humans, human-animal interactions, the intersection of human/animal/environmental health, and the treatment or prevention of zoonotic diseases. Again, such studies will be considered translational only when they include a clear line of sight to translation into human health, including clear articulation of the specific next steps for impact on health to be realized.

**T.5: Bridging Pre-Clinical Development to Initial Human Studies**

T**.**5 research focuses on transformation of concepts and testable prototypes, be they devices, diagnostics, drugs, or data algorithms, into impact on clinical care and health. A central premise of the T**.**5 stage is the recognition that following a linear and unidirectional translational developmental path is fraught with risks and will often fail. Rather, effective T**.**5 translation should be a bidirectional and iterative process. Clinical and real-world considerations must fuse logically with scientific and engineering principles to fine-tune early testing and design sequences so that promising ideas are more likely to reach impactful medical application as rapidly as possible. Successfully traversing this translational stage requires specialized facilities and tools, and close collaboration between scientists, engineers, biomedical researchers, and clinical care providers. T**.**5 research yields knowledge to improve translational potential of basic biomedical discoveries and prototypes.

## T1: From Bench to Bedside

T1 research translates promising laboratory and pre-clinical findings into the care of patients. Examples of T1 research include testing a treatment or preventive measure in humans or testing a diagnostic assay or strategy. Such studies might include proof-of-concept and first testing in humans for promising physiology, toxicity, pharmacokinetics treatments, and other preliminary efficacy studies, as well as evaluation of novel methods of diagnosis. T1 research yields knowledge that demonstrates potential new strategies for treatment, prevention, and diagnosis.

## T2: From Bedside to Clinical Practice

T2 research translates successful applications in humans into wider use in clinical practice in widespread practice, into patient populations, and includes controlled observational studies and clinical trials, survey research, and other approaches to further define the appropriateness of treatments and tests in clinical care. T2 research may yield knowledge about the efficacy of interventions in optimal clinical settings or initial assessments of effectiveness in more generalizable samples.

## T3: From Clinical Practice to Widespread Clinical Practice and Care Delivery

T3 addresses the need to understand whether treatments, diagnostic tests, or other interventions are generalizable to the wider span of clinical practice. This might include clinical trials in broad ranges of settings and conditions, studies that include a comprehensive range of clinical and patient-reported outcomes, community-based participatory research (CBPR), and services research. T3 research seeks to evaluate evidence-based guidelines for improved health care delivery, dissemination strategies, and widespread implementation of care strategies. T3 research yields knowledge about how interventions work in real-world settings, even while following a research protocol for intervention, but focusing on optimizing generalizability to widespread use.

## T4: From Healthcare Delivery to Impact on the Community, on the Public’s Health, and on Public Policy

T4 research translates effective health care delivery into improved community and population health, informs new policies, and includes interventions in and monitoring of populations, the wider dissemination/implementation of improved practices/interventions, and health policy. Examples of T4 include policy analysis and evaluation, cost-benefit analysis, and surveillance studies and research questions focus on the intervention “as used,” rather than according to a research protocol. T4 research yields knowledge that ultimately results in improved health, with research questions focused on the intervention as used in the real world rather than according to a strict research protocol in limited settings.

**Basic Research: Pre-Translational Research**

Basic research (earlier than T**.**5), while a critically important foundation for translational research, is not part of the translational spectrum. It focuses on gaining greater knowledge and understanding of the fundamental mechanisms of biology, disease, or behavior. Basic research yields knowledge about basic biological, social, and behavioral mechanisms and presentations of human disease. While significant healthcare impacts may ultimately arise in the long-term and may even be the primary objective of the work, the path to proximate clinical impact is not explicit, well-defined, nor easily foreseeable.

At Tufts CTSI, we belief that authentic translational research requires a systems approach, which emphasizes interactive, interdependent, and holistic strategies in the development of treatments, that bridges gaps between discoveries at molecular or component levels and interventions that will affect human health at individual or population levels. Translational research should focus on *applied research projects* that *turn findings* from the laboratory, clinic, and community *into treatments and interventions* with the clear potential to have a significant *impact on the health of the public*.

While some ambiguity will persist, these guidelines should allow easier prioritization of T**.**5-T4 translational research and drive priorities for programs. If unclear, researchers are encouraged to discuss specific translational projects with CTSI leadership to determine whether their research falls into the purview of CTSI translational priorities.

**Defining Translational Research in Tufts CTSI Priority Program Areas**

***Comparative Effectiveness Research (CER)*** is the generation and synthesis of evidence that compares the risks and benefits of alternative interventions and methods to prevent, diagnose, treat, and monitor a clinical condition in “real world” settings, or to improve the delivery of care. The purpose of CER is to develop and disseminate evidence-based information about which interventions are most effective for which patients under specific circumstances with the goal of improving health care at both the individual and population levels.

***Stakeholder- and Community-Engaged Research*** includes stakeholders and/or community members as authentic and active partners in all aspects of research. This includes: identifying research needs and priorities, hypothesis development, study design, implementation, analysis, and/or results dissemination. Research which that only includes participants based on affiliation or participation in a stakeholder or community group that is the target of research is not considered stakeholder- and community-engaged research. Stakeholders include (the 7 Ps of Stakeholders[[2]](#footnote-2)):

1. Patients, their families, communities, and the public
2. Providers
3. Purchasers
4. Payers
5. Policy makers
6. Product makers
7. Principal Investigators

Incorporating the perspectives of diverse stakeholders requires meaningful connections, collaboration, and full engagement of all team membership, which we term “broadly-engaged team science[[3]](#footnote-3).” Broadly-engaged team science enhances clinical and translational research relevance and impact, provides the public with a greater return on its investment in research, and promotes public engagement and trust in science.

***Integrating Special Populations*** addresses health disparities or translational research gaps involving: 1) children, 2) elders, 3) minority or underserved populations (e.g., differences in racial, ethnic, gender, or socio-economic status); 4)people living in rural vs. urban environment; and 5) pregnant women; 6) survivors of childhood diseases that are transitioning to adult care; 7) people with disabilities; and 8) “hard-to-reach” groups that are often impacted by health disparities.

***Translational One Health Research*** includes studies of naturally occurring diseases (not induced) shared by animals (wild or domesticated, not laboratory) and humans with the ultimate goal of improving human outcomes. This includes research involving animals with naturally occurring disease that serve as models of comparable human disease, research on human-animal interactions (e.g., animal-assisted therapy, pet ownership) as it relates to the physical and mental health of humans, intersections between human/animal/environmental health, and study of the treatment or prevention of zoonotic diseases transmitted between wildlife or domesticated species and humans.

***Basic One Health*** ***Research***, which may have implications for human health, but does not focus on *developing treatment, clinical practice, or changes in policy to improve human health,* is not considered translational.

**Defining Translational Research Methods for Tufts CTSI**

***Translational Research Methods*** include approaches, procedures, techniques, and tools for addressing and solving translational research questions, problems, or barriers.

Tufts CTSI supports the development of generalizable and broadly applicable translational methods that allow researchers to:

* overcome roadblocks that impede the conduct of clinical and translational research,
* expedite translation of biomedical, psycho-social and economic discoveries into interventions, and
* improve efficiency and quality across the translational research spectrum.

**Clarifying What Translational Research Means for the Tufts CTSI Pilot Studies Program**

**Meeting NIH Program Interests**

The NIH 2013 CTSA Funding Opportunity Announcement (FOA) under which Tufts CTSI is currently funded states that the “intent of the CTSA Translational Pilot Program is to *develop novel methodologies for cost-effective execution of research projects, stimulate interdisciplinary team collaboration on innovative or high risk translational research questions, and test feasibility of novel approaches to translational research*.” The program also provides flexibility for each CTSA to focus on particular priorities of their integrated home with the following restrictions:

1. The program cannot focus on a select disease category, a few diseases or specialties, or on a limited number of investigators
2. The program must not support any clinical trials beyond phase IIA

The NIH 2016 CTSA FOA does not articulate specific program goals for the Pilot Studies Program, but states, *“each CTSA hub has the flexibility to focus and design their translational pilot program to address their particular priorities*.” Consistent with the 2013 FOA, the 2016 FOA stipulates the program must be disease-agnostic, may not support a limited number of investigators or clinical trials beyond phase IIA, and says the program “*should focus on translational and clinical research rather than on basic discovery research*.”

NIH further states pilot research projects should *“not only address a translational research question, but also provide insights that could be generalizable to other projects.”* Outcomes of Pilot Studies Program described in the 2016 CTSA FOA are currently being evaluated at the CTSA Consortium level by the [CTSA Common Metrics Initiative,](https://www.tuftsctsi.org/research-services/research-process-improvement/common-metrics-initiative/) which is assessing whether Pilot Studies resulted in at least one publication with a PMCID number in a peer reviewed journal. While we support this intent, the Tufts CTSI Pilot Studies Program prioritizes generating preliminary data for a project grant application (which is not mutually exclusive of publication).

**Prioritizing Tufts CTSI Pilot Studies Program Goals**

The 2018 Tufts CTSI Pilot Studies Program “seeks proposals for *innovative, high impact, translational science projects with a focus on building interdisciplinary, multi-institutional research teams including investigators from the basic, clinical, and/or applied sciences*.” Applicants are strongly encouraged to focus on one of our Signature Program areas, integrating special populations into research and/or the development of new translational research methods across the T**.**5-T4 spectrum.

A clear focus on funding high-impact, authentic translational research, as opposed to basic research, is critical for Tufts CTSI not only because it is consistent with the NCATS vision for the program, but also because it supports our mission “*to stimulate and promote innovative clinical and translational research, with the goal of improving the public’s health*.” The 2018 Tufts CTSI Pilot Studies Program will be successful if it:

1. initiates translational research in Tufts CTSI priority program areas,
2. builds new interdisciplinary, multi-institutional research teams,
3. generates preliminary data for subsequent translational grant submissions to external funding agencies,
4. disseminates research findings, both positive and negative, through publications, presentations, educational materials, training, etc., and
5. applies findings to patients and populations in the form of new interventions, treatments, devices, practices or policies and demonstrates a measurable impact on health.

**What is sufficient evidence of engagement in an early-stage translational research publication?**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Inclusion in author list** | **Mention in text** | **Mention in acknowledgements** |
| **Patients** | Sufficient | Sufficient if a clear indication is givenof involvement a research activity (e.g., in one of the 20 research activities\* in the engagement map) | Sufficient if a clear indication is givenof involvement a research activity (e.g., in one of the 20 research activities\* in the engagement map) |
| **Providers** | Not sufficient | Sufficient if a clear indication is given that they played a role as a provider (clinician or health system) in a research activity (e.g., in one of the 20 research activities\* in the engagement map) | Sufficient if a clear indication is given that they played a role as a provider (clinician or health system) in a research activity (e.g., in one of the 20 research activities\* in the engagement map) |
| **Payers** | Not sufficient | Sufficient if a clear indication is given that they played a role as a payer in a research activity (e.g., in one of the 20 research activities\* in the engagement map) | Sufficient if a clear indication is given that they played a role as a payer in a research activity (e.g., in one of the 20 research activities\* in the engagement map) |
| **Purchasers** | Not sufficient | Sufficient if a clear indication is given that they played a role as a purchaser in a research activity (e.g., in one of the 20 research activities\* in the engagement map) | Sufficient if a clear indication is given that they played a role as a purchaser or health system) in a research activity (e.g., in one of the 20 research activities\* in the engagement map) |
| **Product makers** | Not sufficient  | Sufficient if a clear indication is given that they played a role as a product maker in a research activity (e.g., in one of the 20 research activities\* in the engagement map) | Sufficient if a clear indication is given that they played a role as a product maker in a research activity (e.g., in one of the 20 research activities\* in the engagement map) |
| **Policy makers** | Not sufficient | Sufficient if a clear indication is given that they played a role as a policy makers in a research activity (e.g., in one of the 20 research activities\* in the engagement map) | Sufficient if a clear indication is given that they played a role as a policy makers in a research activity (e.g., in one of the 20 research activities\* in the engagement map) |
| **Principal investigators** | Not sufficient | Sufficient if a clear indication is given that there are multiple disciplines involved or collaborations from different types of researchers  | Sufficient if a clear indication is given that there are multiple disciplines involved or collaborations from different types of researchers |

NOTES: \*the 20 research activities are listed in Table 1, Column 2.

1. Zerhouni EA. Translational and Clinical Science – Time for a New Vision. N Engl J Med. 353:1621-1623. 2005 October. PMID: 16221788 [↑](#footnote-ref-1)
2. Concannon TW, Meissner P, Grunbaum JA, et al. A new taxonomy for stakeholder engagement in patient-centered outcomes research. J Gen Intern Med. 2012 Aug; 27(8): 985-991. [↑](#footnote-ref-2)
3. Selker HP, Wilkins CH. From community engagement, to community-engaged research, to broadly engaged team science. Journal of Clinical and Translational Science. 2017; 1(01): 5-6. [↑](#footnote-ref-3)