Beyond Translational Research from T1 to T4: Beyond "Separate but Equal" to Integration (Ti)

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Not long ago, the worlds of academic medicine and biomedical research were segregated into laboratory researchers and clinical researchers. Not only were they separate, they were seen as not quite equal: typically the greatest respect was accorded to laboratory research, seen as the fount of innovation and breakthroughs, supported by investigator-initiated R01 grants from the National Institutes of Health (NIH) and analogous grants.

However, over the past two decades has grown a sense that this research world order was out of balance. The increasingly evident failure of biological discoveries to translate into impact on health led to interest in enhancing the clinical research enterprise. There grew an appreciation that clinical research also had investigator-initiated research at its innovative core, and that its spectrum was far wider than often appreciated. A report of the Association of American Medical Colleges (AAMC) in January 2000[1] emphasized the need for advancing clinical research as a discipline, and that it includes a wide variety of disciplines, including clinical epidemiology and health services and policy research. At the same time, NIH began supporting rigorous training and career development in clinical research by its K30 Clinical Research Curriculum Awards, K23 career development awards, and K24 clinical research mentoring awards. Long-standing and new organizations began advocating for better support of, and career development in, clinical research, and NIH and foundations began paying more attention to clinical research and its component disciplines.

This path might have ultimately led to "separate but equal" attention and support for clinical research and bench research, but then "translational research" was injected into this evolution by NIH's creation of the Clinical and Translational Science Award (CTSA) program. "Separate but equal" was set aside to make way for *integration* as "clinical and translational science." With this focus on translation of basic biomedical research into advances in health came the identification of the "translational blocks" that must be surmounted to have ultimate impact on health. Research must cross an initial block, at "T1," from bench to bedside, then "T2," from bedside to practice, and then "T3" and "T4," to generally available medical care and public health measures and policy. This new taxonomy and linked reframing of the biomedical research enterprise, exemplified by CTSAs, was more than just relabeling. Researchers were redefining their roles to include active translation of biomedical insights into improved health of the public. Accordingly, the metric of the quality of research is evolving from solely being represented by the prestige of the funding source and the journal in which it is published to also include whether it represents a discernible translational step that leads to improved health. Conversations about research now include a focus on having an ultimate, and ideally proximal, impact on the health of the public.

However, although these translational steps represent an important heuristic, to fulfill the translational objective, we need to move beyond T1–T4; *we now must integrate the Ts*. We must weave together these translational steps into a single adaptive process. For example, we might integrate "efficacy" and "effective" trials. We understand the need for detailed *efficacy trials* to assess a treatment's optimum impact in selected patients under idealized conditions, typically for short periods, for Food and Drug Administration (FDA) approval. We also understand the need for *effectiveness trials*, to test a treatment under usual practice conditions, across the spectrum of patients for whom it will ultimately be used, with follow-up that more closely matches the long durations that patients use medications. But must these trials be separate? For example, as an integrated alternative approach, if during an *efficacy* trial, a positive effect was seen and ratified by the data safety monitoring board (DSMB), could the trial then transition directly to an *effectiveness* phase? Thereby, while the FDA approval process is underway and publication pending, rather than disassembling the operating trial infrastructure, could the entry criteria be immediately widened and settings added so that the effectiveness trial could proceed without delay, and could potentially be complete near the time of FDA approval? Besides providing a broader understanding of the treatment, it would support the opportunity to understand heterogeneity of treatment effects for special patient groups. The continued involvement of the efficacy trial infrastructure could facilitate collecting data to help understand underlying biological, including genetic, mechanisms. Further, during the effectiveness phase, plans for enhanced use and dissemination of the results could be devised, such as multivariable predictive models to support the treatment's optimal use in those patients most likely to benefit. The net result of integrating earlier and later translational steps—the next step beyond the identification of the translational steps—should be a better and more rapid translation of research results into an impact on the public.

This is conceptually only evolutionary, but the implications for the logistics and team composition for research are potentially revolutionary. The *current* discontinuous approach that roughly follows the T1–T4 steps is inefficient and slow: Following identification of a potentially promising new drug, a T1–T2 researcher might propose to assess the safety and efficacy of a new drug in early clinical trials and targeted efficacy trials. If that succeeds, approval and publication may follow. Then, potentially years later, upon reading the literature, others with experience and infrastructure for running effectiveness trials might apply for, and later might receive, funding for a generalizable trial—or not. If

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getting to that stage, they might or might not have the involvement of the original investigators, and thus might or might not collect key data to inform understanding of the heterogeneity of effects in various subgroups. And these investigators may or may not have involvement of those who could provide predictive models and other forms of decision support to facilitate translation into widespread use. Instead, we should develop an alternative model. From the outset, to support a continuous and fully informed translational research process, the evaluation of treatments should be by integrated teams with the capacity to take on an integrated translational process.

This is a different model than we use now, and it poses design, logistical, analytic, regulatory, funding, and other problems. CTSAs have some of the pieces needed for this approach, but they still generally lack the integrated processes needed for this model to work. How such models might be devised and created, and how they might be supported, remain important questions. Models that will respond to this need will integrate the translational steps and their currently disparate research teams. This will be challenging in many dimensions. However, it must be done. Separate but equal components of biomedical research will not solve the need for translating biomedical research into health; it is time for translational integration, "Ti." CTS

References

1. Ensuring the Future of Clinical Research. Association of American Medical Colleges. Vol. January 2000. Washington, DC. (Ralph Snyderman, Chair.)