Lessons From COVID-19 on the Stepwise Development of Interventions

Edelle Field-Fote, *Emory University*

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Lessons From COVID-19 on the Stepwise Development of Interventions

Edelle [Edee] Field-Fote, PT, PhD, FASIA, FAPTA
Editor-in-Chief
edee@miami.edu

At the time that I write this, the world is in the grip of the COVID-19 disease pandemic. As you likely have heard more times than you care to count by now, the viral agent causing this disease is related to the virus that causes severe acute respiratory syndrome (SARS), and for that reason the virus is officially called SARS-CoV-2. The CoV indicates that the virus is a member of the Coronaviridae family, whose name is derived from the spike- or crown-like appearance of the surface proteins that are visible under an electron microscope.

As you have probably also heard many times, a vaccine for this virus is likely to be at least a year in development. Given that this vaccine represents a determined worldwide endeavor with billions of dollars being poured into the effort, like me, you may have been curious about the reason for this extended time frame for the vaccine development process. In tracking down the answer to this question, I was struck by the similarities between the history and process of vaccine development and that of the development of neurologic physical therapy interventions.

Vaccines have advanced tremendously since the first-generation approaches that represent the types of vaccines we received as children. In these earliest, whole-pathogen vaccines, injection of small amounts of attenuated or inactivated virus activates the immune system, triggering the development of antibodies that protect us against infection. Second-generation, subunit vaccines, rather than being based on whole viruses, involve only the antigens that activate the immune system. Finally, third-generation, nucleic acid vaccines involve injection of plasmid with the encoding gene of the desired antigen to induce the immune system to express antibodies.[1,2] Each of the 3 forms of vaccines is of value, and their utility depends on the viral target.

There are striking parallels between the evolution of vaccine development and the evolution of neurologic physical therapist practice, with our conventional, contemporary, and emergent approaches. One might consider conventional interventions that target compensation to be our first-generation approaches. The more contemporary, task-specific training interventions intended to promote restoration through use-dependent plasticity would be our second-generation approaches. Lastly, emergent interventions that combine neuromodulation with training interventions designed to promote use-dependent plasticity could be thought of as our third-generation approaches.

Despite the similarities in the evolution of vaccine development and the advancement of neurologic physical therapy interventions, there are conspicuous differences in the processes of investigating the value of these respective classes of interventions. Vaccines undergo the stepwise process used with almost all other pharmacologic and biologic interventions. In the vast majority of cases, prior to being made available on a broad scale, they progress from basic mechanistic studies through small phase 1 safety studies to moderately sized phase 2 dose-response studies to large phase 3 randomized clinical trials.

For various reasons, the advancement of neurologic physical therapy interventions has mostly followed a different path. Our conventional, first-generation physical therapy treatments primarily arose from a trial-and-error approach in the clinical setting and were passed along as part of our academic and clinical training. Second-generation physical

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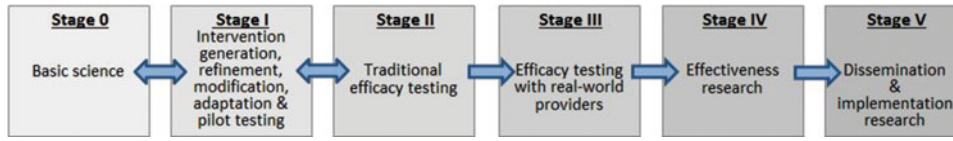

Figure. The NIH Stage Model has high relevance for the development of rehabilitation interventions. While not shown in the figure, the stages are highly iterative and recursive, wherein evidence may show the need to return to prior stages before proceeding.

therapy treatments had a foundation in basic science studies of neuroplasticity and use-dependent neural reorganization.[3,4] Emerging, third-generation treatments build on second-generation treatments, adding various forms of neural stimulation to augment the electrical changes that underlie neural activation and thereby enhance neuroplastic effects of training. The progression of neurologic physical therapy approaches has lacked a stepwise approach. Progress has mostly been based on small studies that often lack conclusive evidence; issues of dose-response relationships have been largely unexplored.

The reasons underlying the differences in progression of pharmacologic/biologic interventions and rehabilitation interventions are many and varied. Studies of physical therapeutic interventions require large commitments of time from both participants and study personnel. Needless to say, the deliverables from these studies are not of the type that attract the interest of industry sponsors. However, the cadre of neurologic physical therapists who have gone on to acquire research training has grown steadily, as has our competitiveness in the acquisition of federal grant funding.

Leaving aside the language of clinical trial phasing that is used in the development of pharmacologic/biologic interventions, I believe we have a valuable opportunity to learn from our investigator colleagues in the behavioral sciences, for whom the National Institutes of Health (NIH) Stage Model serves as their framework for intervention development.[5] The NIH Stage Model "is an iterative, recursive, multidirectional model of behavioral intervention development" with 6 stages (see Figure). Beginning with basic mechanistic studies (Stage 0) and progressing next to intervention refinement (Stage I; which may include dose-response assessment). The model emphasizes that the development of an intervention has been accomplished only when it can be implemented in a way that maximally meets the needs of the group for which it is intended (Stage V).

The NIH Stage Model offers a common language for intervention development research. It allows conceptual questions to be asked about where an intervention falls in the development cycle and whether the research has appropriately addressed each of the important milestones in that development. With this common language, stakeholders, clinicians, investigators, reviewers, and funding agencies can have meaningful conversations about the appropriate next steps that are needed before an intervention is ready to be applied in the clinical setting. Abiding by this model also ensures the research evidence exists to justify reimbursement when that time comes. Our patients and profession will surely benefit if we join with our behavioral research colleagues and embrace the NIH Stage Model as we pursue the development of neurologic physical therapy interventions.

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