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Leveraging Vascular Access Clinical Trial Endpoints to Enhance Innovation

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Dialysis vascular access is currently both the "Lifeline" and the "Achilles Heel" of hemodialysis.[1,2] Arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs) have an unassisted primary patency of < 50% at 6 months and 23% at 1 year, respectively, due to venous segment stenosis, while tunneled dialysis catheters (TDCs) have a very high incidence of infection, thrombosis, and central venous stenosis.[3] These complications result in a very significant degree of morbidity, mortality, and economic cost (approximately $5 billion USD per annum).[4] Unfortunately, despite the magnitude of the clinical problem, there are currently no truly effective therapies for dialysis vascular access dysfunction. Why is this the case?

An important prerequisite for a robust product development pathway is the acceptance by all relevant stakeholders (patients, health professionals, regulators, payors, and industry partners), on a set of clinical trial endpoints. Until recently, however, this was nonexistent in the vascular access arena. A potential reason for this was that all the different "physician" stakeholders had very different perspectives on what constituted vascular access success. For a radiologist, a good endpoint for success was the documentation of good flow on an immediate postangioplasty angiogram (regardless of later recoil). For a surgeon, it was a lack of thrombosis. For a nephrologist, it was the ability to obtain adequate dialysis—and I don't think that anyone had actually asked patients about what they considered to be most important about *their* vascular access! This divergence of opinion among key stakeholders clearly resulted in a poorly defined product (drug, device, or biologic) development pathway for dialysis vascular access, which then unfortunately drove the three I's (Interest, Innovation, and Investment) *away* from vascular access.

As an attempt to address this significant unmet need in the product development pathway for vascular access, the Kidney Health Initiative (KHI), a public-private partnership between the FDA & the American Society of Nephrology (ASN), recently completed a project on the identification of clinical trial endpoints for vascular access. In keeping with the overall ethos of the KHI, the governance for this project (Figure 1) included a core committee (in order to be nimble) and a multidisciplinary steering committee (in order to be inclusive). The heart of the project, however, was a set of three content development teams (CDTs) for AVFs, AVGs, and TDCs. All three CDTs were multidisciplinary by nature and included surgeons, radiologists, nephrologists, infectious disease physicians, nurses, regulators, and industry partners. During the committee deliberations, we tried our best to ensure the patient's voice was kept front and center throughout the discussions.

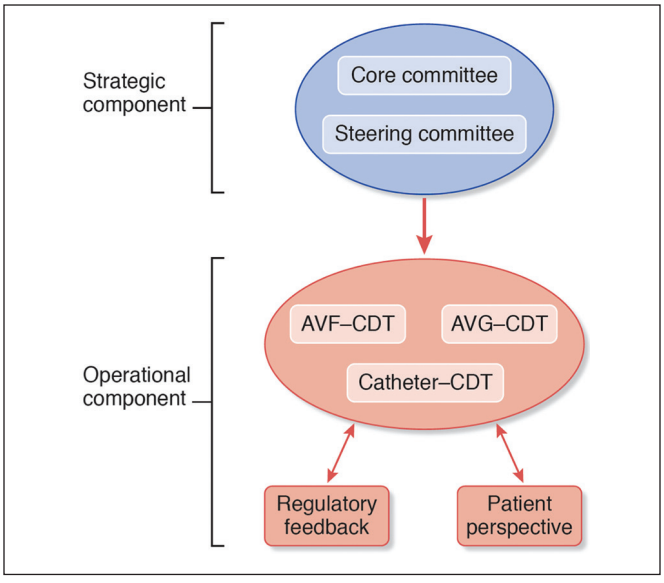

Figure 1. Governance of the KHI vascular access clinical trial endpoints project.[8]

The deliverable from this project was a set of four manuscripts: an introduction, a piece on endpoints for arteriovenous access, a document on clinical trial endpoints for TDCs, and, finally, the FDA's perspective on the first three manuscripts.[5-8]

The manuscript on arteriovenous access, in particular, lays out the framework for clinical trial endpoints for AVFs and AVGs. As described in Figure 2, five different life cycle phases for arteriovenous access were identified: creation, maturation, initial clinical use, sustained clinical use, and dysfunction. These phases were then used to define clinical trial endpoints. Thus, if the focus of a new product was to enhance the creation of an arteriovenous access, then the

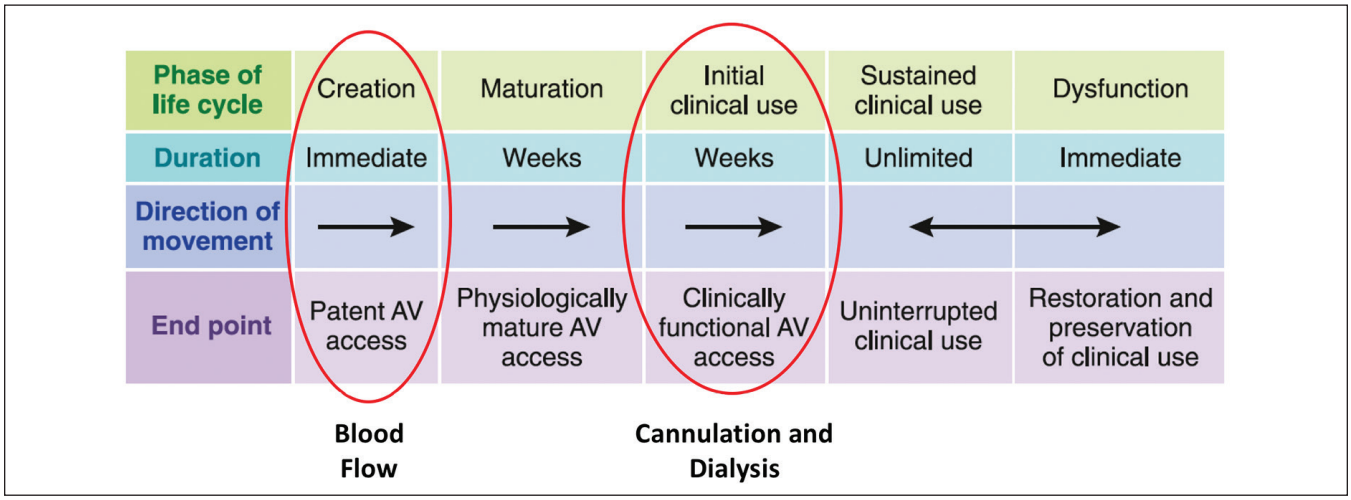

Figure 2. Phases of arteriovenous dialysis access.[7]

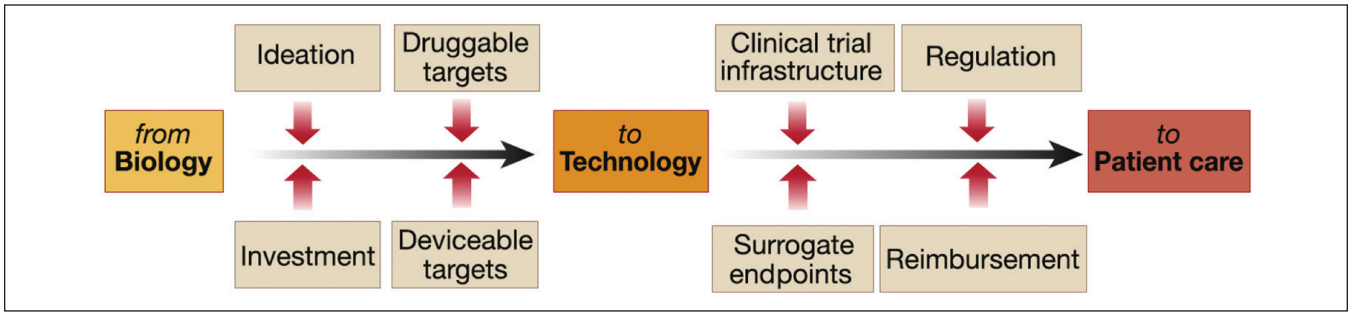

Figure 3. Creating an innovation substrate for dialysis vascular access.[9]

clinical trial endpoint for this product would be the demonstration of a patent arteriovenous access (blood flow). On the other hand, if the focus of a new product was to increase the chances of clinical use of the arteriovenous access, then the endpoint would need to be a clinical endpoint that documented the presence of a clinically functional arteriovenous access (successful cannulation and suitability for dialysis).

The ultimate hope is that the presence of a set of clinical trial endpoints that the vascular access community can agree upon will result in more innovative and effective products coming into the vascular access arena, with a subsequent reduction in the morbidity, mortality, and economic cost associated with dialysis vascular access dysfunction and an improvement in the quality of life of hemodialysis patients.

We were also very cognizant that the identification of clinical trial endpoints is just one piece of a much larger construct that aims to create an *innovation substrate for vascular access*. This innovation substrate needs to start with a better understanding of the biology of vascular access dysfunction. This could then result in *technologies* capable of specifically targeting this biology and thus charting an avenue toward development of patient-centered therapies for vascular access dysfunction (Figure 3).[9]

Last but not least, the presence of a large number of innovative therapies for vascular access dysfunction could allow us to move away from the current *one-size-fits-all paradigm* to a more individualized care pathway, where specific therapies are used in particular patient subsets only: a precision medicine approach to vascular access care! ■

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