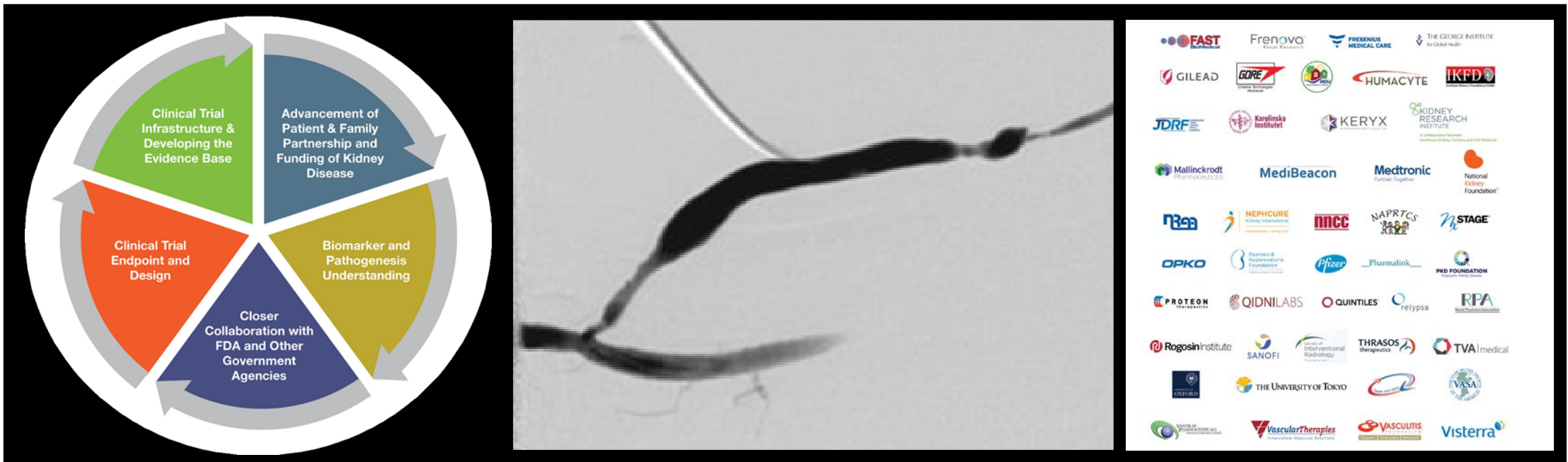


The Kidney Health Initiative: Fostering Innovation in Vascular Access

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Outline

- **Kidney Health Initiative**
- **Vascular access clinical trial endpoints**
- **Why we feel this will make a difference to the vascular access field**

Kidney Health Initiative

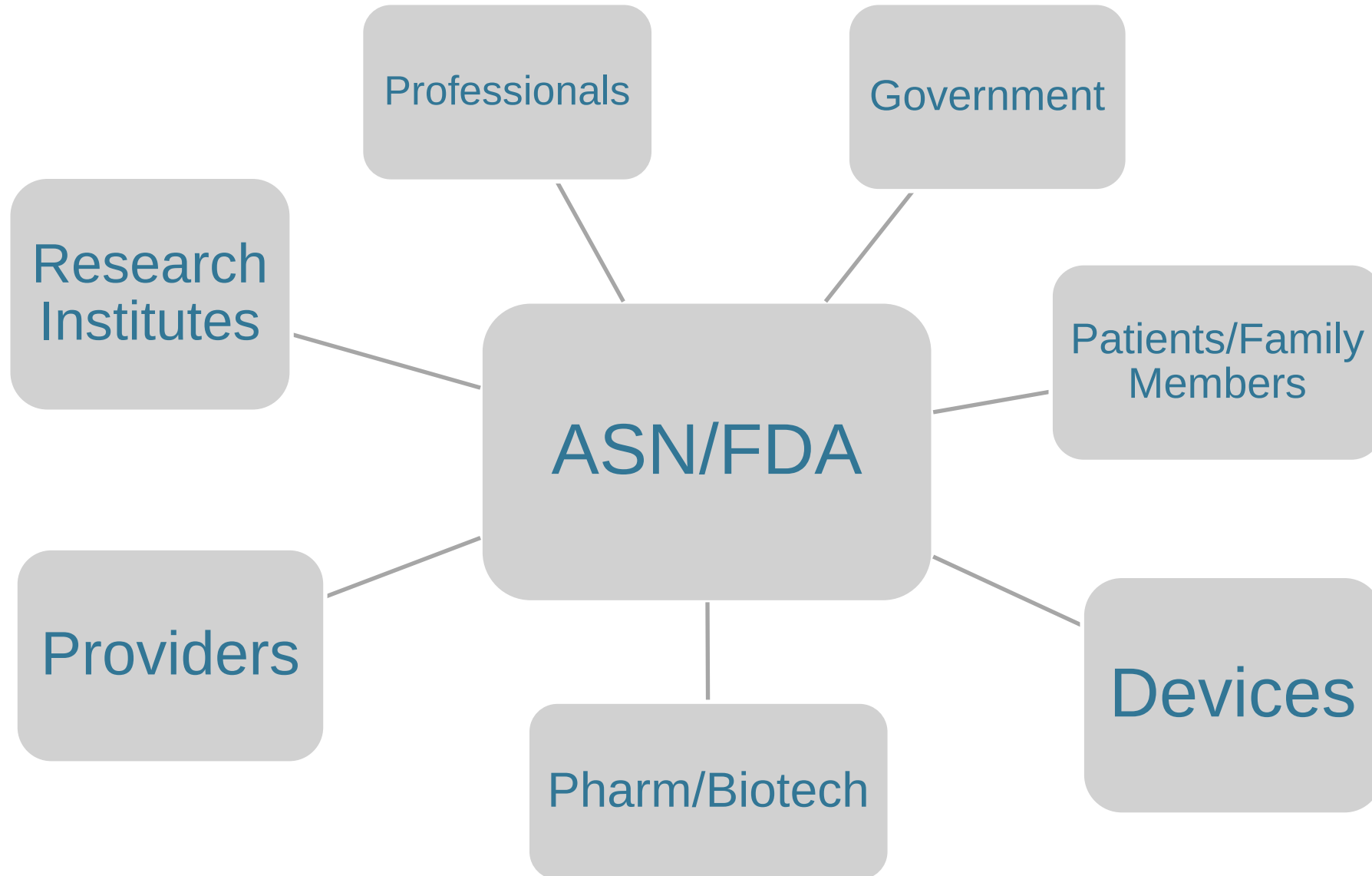
- **Public Private Partnership between the FDA and ASN**
- **Formed in September 2012**
- **Goal of promoting innovation and patient safety in kidney disease**



Multi-disciplinary collaboration of over 80 organizations



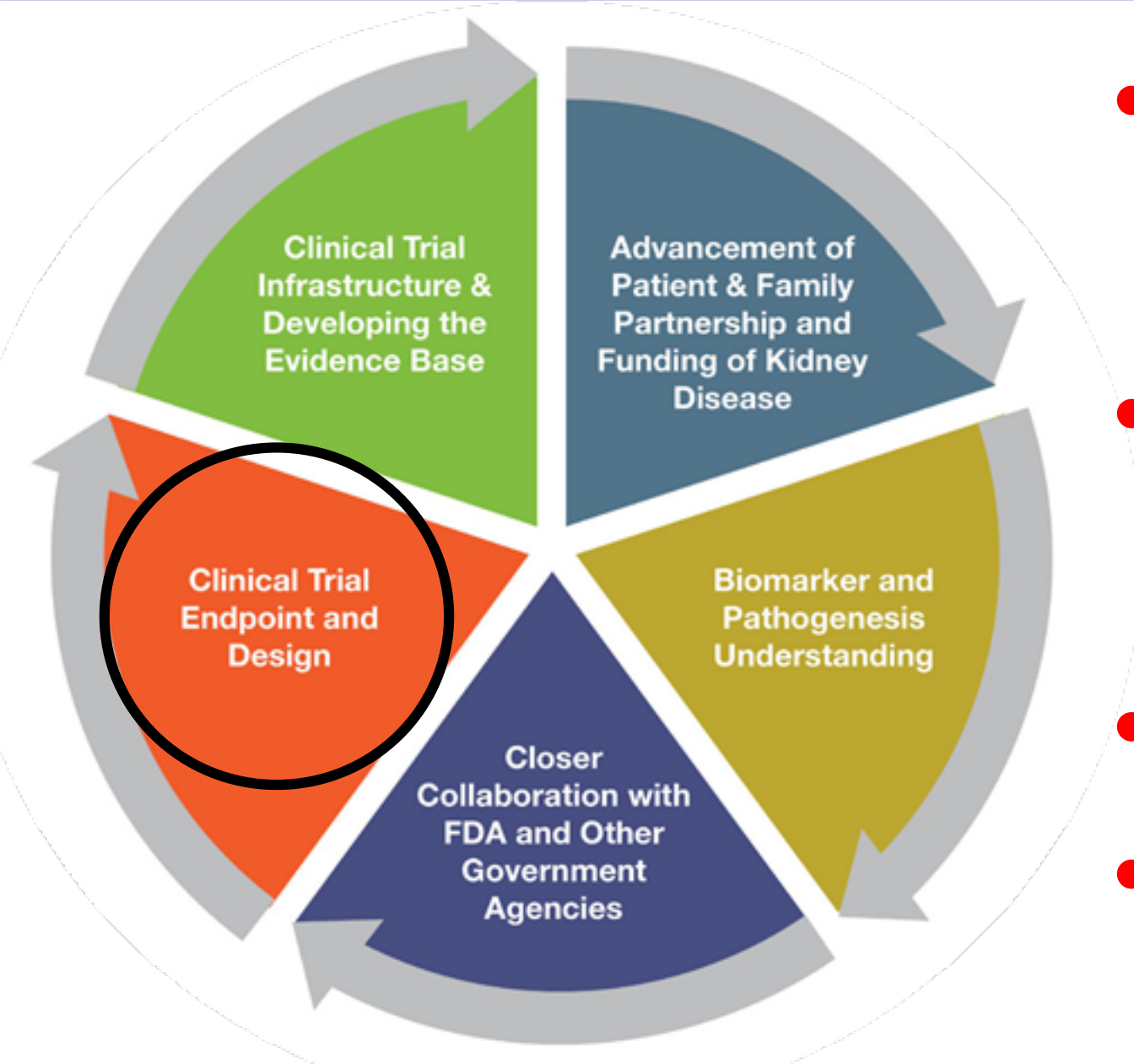
KHI is a collaborative effort



Multi-disciplinary collaboration of over 80 organizations



Making an impact: projects in strategic priority areas

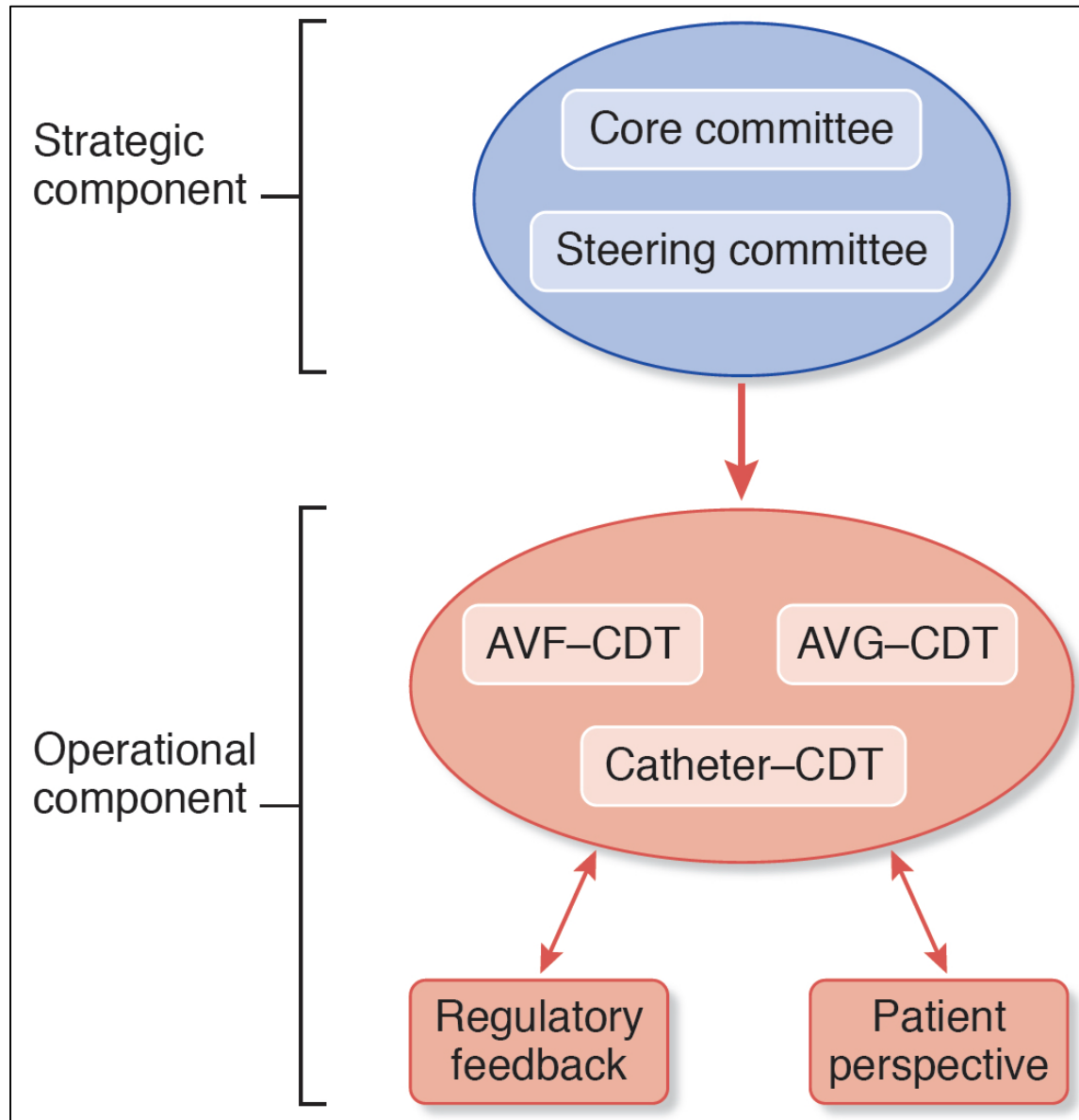


- **White papers, data standards, workshops or a roadmap**
- **Facilitate the passage of drugs, devices and biologics into the kidney area**
- **Over 15 projects to date**
- **Clinical trial endpoints for vascular access**

The Rationale...

- **Dialysis vascular access is both the “Lifeline” and the “Achilles Heel” for hemodialysis patients**
- **Lack of effective therapies**
- **Poorly defined product development and regulatory pathway**
- **A lack consensus on clinical trial endpoints for success**
 - **Radiologist = Technical patency**
 - **Surgeon = Primary patency (lack of thrombosis)**
 - **Nephrologist = can the patient be dialyzed**
 - **Patient = has anyone asked me??**

Organizational level



- **Small Core Committee (operationally nimble) and a large Steering Committee (inclusive)**
- **Constituted 3 multi-disciplinary (industry and health professionals) Content Development Teams**
- **Regulatory agencies (FDA)**
- **Patients**
- **Innumerable conference calls and two face to face meetings**

Deliverable

Clinical Trial End Points for Hemodialysis Vascular Access

Background, Rationale, and Definitions

Definitions and End Points for Interventional Studies for Arteriovenous Dialysis Access

Gerald A. Beathard, Charmaine E. Lok, Marc H. Glickman, Ahmed A. Al-Jaishi, Donna Bednarski, David L. Cull, Jeffery H. Lawson, Timmy C. Lee, Vandana D. Niyayar, Donna Syracuse, Scott O. Trerotola, Prabir Roy-Chaudhury, Surendra Shenoy, Margo Underwood, Haimanot Wasse, Karen Woo, Theodore H. Yuo, and Thomas S. Huber

Recommended Clinical Trial End Points for Dialysis Catheters

Michael Allon, Deborah J. Brouwer-Maier, Kenneth Abreo, Kevin M. Baskin, Kay Bregel, Deepa H. Chand, Andrea M. Easom, Leonard Mermel, Michele H. Mokrzycki, Priti R. Patel, Prabir Roy-Chaudhury, Surendra Shenoy, Rudolph P. Valentini, and Haimanot Wasse

FDA Regulatory Perspectives for Studies on Hemodialysis Vascular Access

Frank P. Hurst, Robert E. Lee,* Aliza M. Thompson,[†] Brian D. Pullin,* and Douglas M. Silverstein**

Arteriovenous dialysis access: **Phases**

Phase of life cycle	Creation	Maturation	Initial clinical use	Sustained clinical use	Dysfunction
Duration	Immediate	Weeks	Weeks	Unlimited	Immediate
Direction of movement	→	→	→	↔	→
End point	Patent AV access	Physiologically mature AV access	Clinically functional AV access	Uninterrupted clinical use	Restoration and preservation of clinical use

Blood Flow

Cannulation and Dialysis

**End Point, the clinical setting and the intervention
all have to be linked to each other**

Dialysis Catheters

- **CRBSI**
- **Catheter dysfunction**
- **Central venous stenosis**
- **Emphasizes existing uncertainty in these areas**

Dialysis Catheters: unanswered questions

Table 1. Proposed high-priority studies regarding dialysis catheter end points

CRBSI

Studies to evaluate whether dialysis bloodline cultures are suitable alternatives to direct peripheral venipuncture samples; to facilitate such studies, we propose that future FDA approval studies of suspected catheter infection in patients receiving HD obtain peripheral blood cultures in a subset of patients enrolled to assess their agreement with bloodline cultures, with enough power to adequately address the issues of sensitivity, specificity, and positive and negative predictive value of such cultures

Studies to evaluate the use of differential time to positivity or proportional quantitative growth of bloodline and catheter hub blood cultures in HD catheters both before and after initiation of an HD session

Studies to assess the predictive value for CRBSI of different temperature thresholds in patients on HD

Studies to assess whether CVC intraluminal colonization in asymptomatic patients on dialysis precedes most CRBSI cases and whether it may be a reliable surrogate outcome for future studies (20)

Catheter dysfunction

Studies to evaluate the variability of dialysis blood flows between consecutive HD sessions; catheters should be matched for design variables, such as luminal radius and catheter tip designs

Studies to evaluate the optimal method to document whether the catheter tip is in the right atrium (19); also, tip orientation is important for step tip catheters, because they do not function optimally if the arterial port (short end) is against the venous wall

CRBSI, catheter-related bloodstream infection; FDA, Food and Drug Administration; HD, hemodialysis; CVC, central venous catheter.

Dialysis Catheters: secondary endpoints

Table 2. Proposed secondary outcomes in dialysis catheter trials

Catheter dysfunction

Use of thrombolytic therapy

Antimicrobial resistance—not just of clinical isolates but also of surveillance cultures

Catheter removal

All-cause hospitalization or hospitalization due to infection

Systemic antimicrobial use/exposure

Death

Any adverse events directly related to the drug on the patient or catheter integrity

Cost of care

Quality of life

KHI vascular access end points: What they can do...

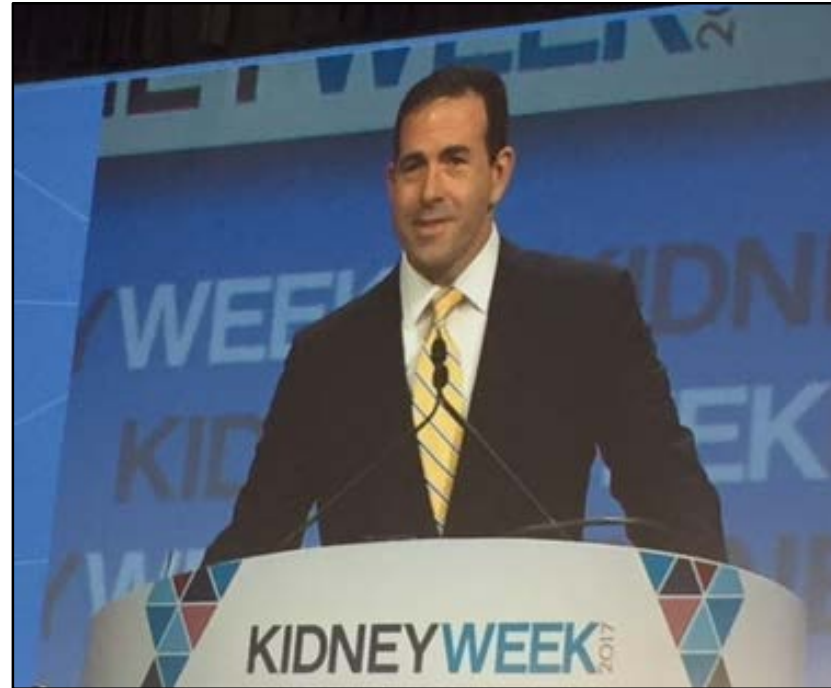
- **Catalyst to enhance innovation in this field**
- **More attractive to industry and academia to enter this field**
- **Generate investment in this area**
- **Develop better therapies for our patients with vascular access dysfunction**

KHI vascular access end points: **What they cannot do...**

- **Not guidance documents**
- **Do not create surrogate end points**

Vascular access end point project could feed into Kidney X

- Kidney X is a partnership between HHS and ASN to create a Kidney Innovation Accelerator
- Goal is to provide non diluted seed funding through challenge competitions in the kidney disease area
- Vascular Access End Point documents attract both new and established players into the vascular access field
- Kidney X could then be a source of funding for vascular access innovation (**implementing arm**)



Take home message!!

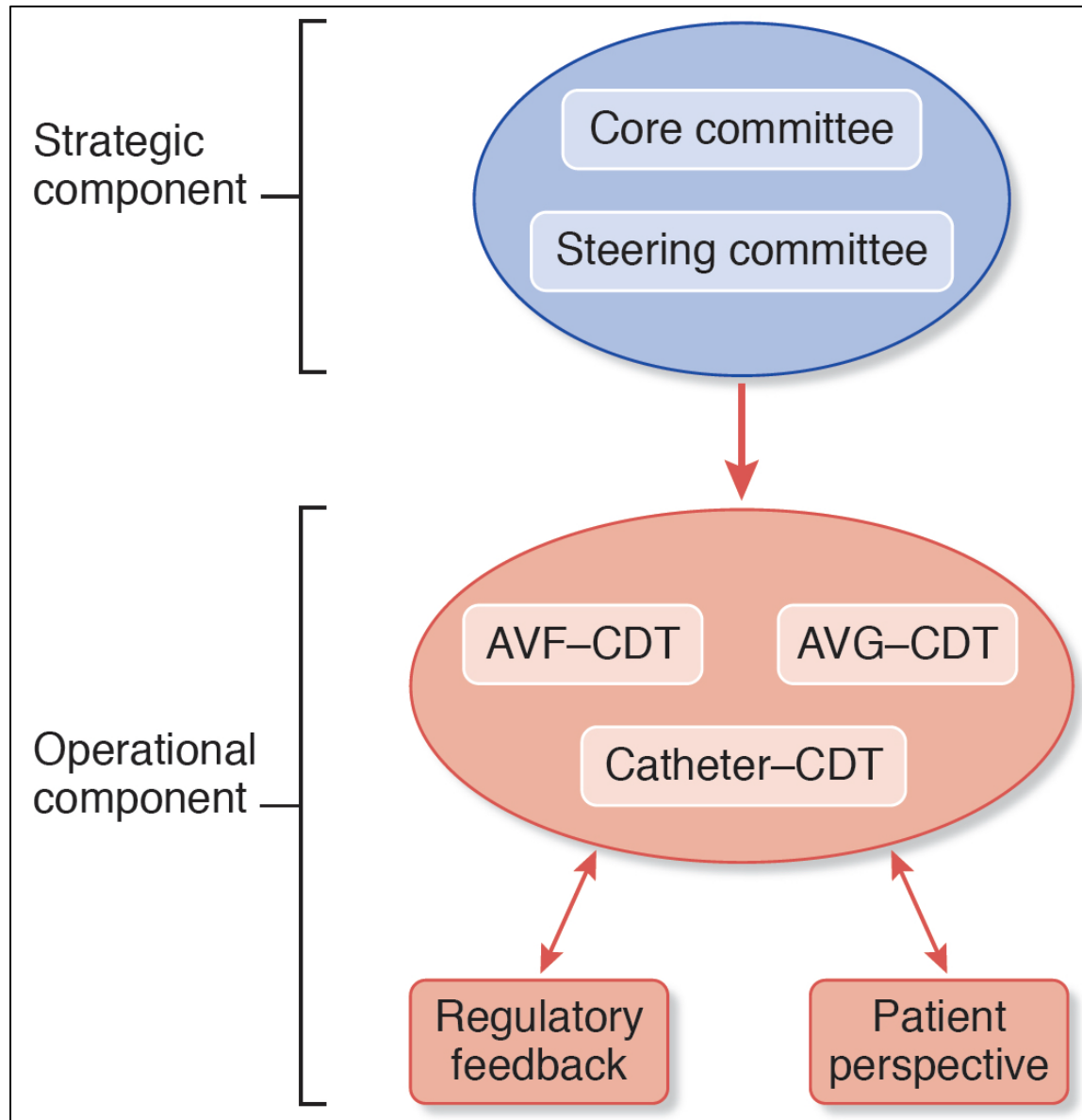


- Significant progress can be made if you provide a platform/meeting place for **collaboration** between industry, academia, patients and regulatory agencies
- KHI Vascular access clinical trial end points project is an example of such a platform

Participants

- Suren Shenoy and Monnie Wasse (Co-chairs)
- Gerald Beathard and Tom Huber (AVF co-chairs)
- Charmaine Lok and Marc Glickman (AVG co-chairs)
- Mike Allon and Debbie Brouer (Catheter co-chairs)
- All the members of the workgroups and the steering committee
- FDA participation: Frank Hurst, Robert Lee, Brian Pullin, Aliza Thompson

Organizational level



- **Small Core Committee (operationally nimble) and a large Steering Committee (inclusive)**
- **Constituted 3 multi-disciplinary (industry and health professionals) Content Development Teams**
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- **Patients**

Arteriovenous dialysis access: End points

Clinical significance	Minimum —————→ Maximum		
Failure AV access creation Success	Stage 1 Nonpatent AV access Patent AV access	Stage 2 Nonmature AV access Physiologically mature AV access	Stage 3 Nonfunctional AV access Clinically functional AV access
Diagnostic criteria			
Direct	Demonstration of blood flow using imaging modality	—————	Cannulate with two dialysis needles for 75% of dialysis sessions within a 4-week period and achieve the prescribed dialysis
Indirect	Presence of pulse, thrill, or bruit on physical exam	AVF Flow ≥ 500 ml/min and Internal diameter > 0.5 cm AVG Flow ≥ 600 ml/min	—————

Dialysis Catheters: CRBSI

