What Is Optimal For FDA Approval Of Novel Vascular Access Devices: Single Arm Clinical Trials Are Adequate To Support Approval Of Novel Vascular Access Devices

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Disclosures

- Speaker for WL Gore
- Scientific advisor, WL Gore
- Consultant, speaker for Merit Medical
- Speaker for 3M/KCI
- Dialysis Access section editor for UpToDate
- PI and steering committee member for Venostent
- PI for InnAVasc trial

The essence of this debate:

Who is best positioned to help patients understand the benefits and risk of an innovative device?

One Retired Clinician at the FDA

-or-

The Field of Practicing Dialysis Access Clinicians

Breakthrough Devices

The Breakthrough Devices Program is intended to provide patients and health care providers with timely access to medical devices by speeding up development, assessment, and review for premarket approval, 510(k) clearance, and De Novo marketing authorization. Breakthrough Devices must meet the FDA's rigorous standards for device safety and effectiveness in order to be authorized for marketing. The Breakthrough Devices Program ***reflects our commitment to device innovation and protecting the public health****.*

www.FDA.gov

FDA Statutory Mandate for Breakthrough Devices:

Probable **Benefit Outweighs the** ***Probable*** **Risk***
Data plan must be the ***least burdensome*** **approach**

Statutory threshold is . . .

But FDA desires this . . .

FDA desire for *reasonable assurance* of benefit through demanding RCTs tends to be *unreasonable* and *overburdensome*, as well as inconsistent

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications Guidance for Industry and Food and Drug Administration Staff., p6. www.FDA.gov

But doesn't everybody love an RCT???

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3. Difficult to design an RCT on truly new devices without surgical or interventional experience with the device to understand:
   - Patient selection
   - Optimal procedural technique
   - Clinical value (ie ideal endpoints)
   - Fit within the treatment algorithm

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4. Devices are not drugs, surgeons can see the impact patient to patient
5. The field can weigh the benefits for the device, leverage their willingness to purchase, and force companies to run the RCTs if necessary

EndoAVF FDA Single-Arm Study Success Spawned Influx of Investment into New Innovation in Dialysis Access

	WavelinQ	Ellypsis
Studied Procedure	Dual catheter w/upper arm Brachial artery access	Single-catheter, two-stage procedure
Submitted Data	Multiple OUS Single-arm data	One US Single-arm study
Safety	8% complication rate (mainly brachial artery access)	2% complication rate
Potential Benefit	Reduced Intervention	Improved Functional Success
Company status	Acquired by BD	Acquired by Medtronic

Current Practice

	WavelinQ	Ellypsis
Current procedure	Off-label arterial access from the wrist	Single-stage with intraoperative PTA
Current use	Highly selected patients by a few operators	Selected patients by a few operators
% Use >6 years	1%	2%

Despite significant safety concerns these technologies were approved and clinicians and patients determined their role in the field

U.S. VasQ Pivotal Study: Primary Endpoint Met

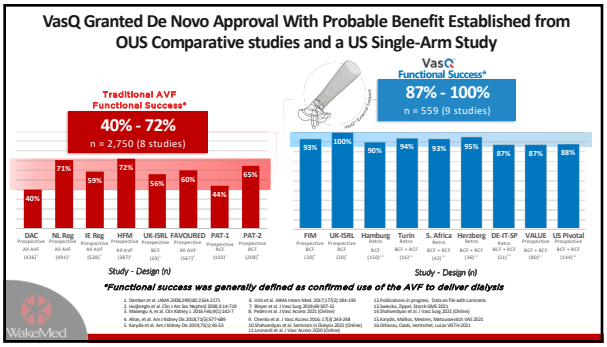
VasQ met the US study primary endpoint of improved primary patency at 6-months

Primary Endpoint
Patency at 6-months (CI- 56%-73%)

Data Safety Monitoring Board Conclusions
- ✓ No safety concerns for patients
- ✓ No device-related permanent damage to patients
- ✓ No increased risk of any safety endpoints
- ✓ No new risks that prevent successful AVF intervention if needed

PG[1-5] VasQ

VasQ Granted De Novo Approval With Probable Benefit Established from OUS Comparative studies and a US Single-Arm Study



*Functional success was generally defined as confirmed use of the AVF to deliver dialysis

Absent U.S. RCT, FDA Took ~2 Years to Decide

Submission Process
- Submitted 2022, FDA requested
  - Full 2 year follow-up
  - Generation of comparative US data
- Provided in Fall of 2023
  - Retro comparative chart review confirmed primary endpoint
  - Matched claims comparison demonstrated significant improvement in primary patency, intervention rate and functional success
- Approval granted in Fall of 2024

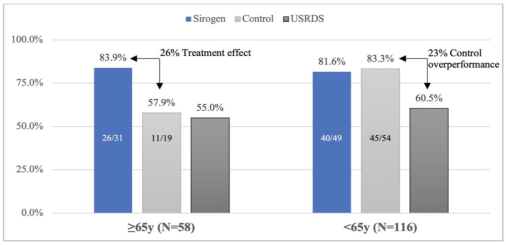
Cost of Delays
- Laminate forced to downs 18 to 3 team members
- Millions of $$ in additiona investment
- ROI dilution from existing investors
- Other companies resorting to an RCT to avoid such risks
- *Withholding of patient opportunity for a safe device with potentially better outcomes*

Sirogen

- In 2021 Vascular Therapies concluded a US multicenter RCT
- 243 patients randomized 1:1 to the Sirogen wrap vs standard AVF
- No instances of device failure
- No safety events or concerns
- Primary endpoints of fistula use or fistula maturation (if not on dialysis) at 150 and 330 days after procedure, as well as secondary patency were not significantly different in the overall study population between treatment and control groups

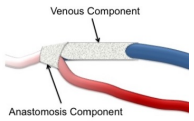
DeVita, Maria et al. On behalf of the ACCESS Trial Investigators. ACCESS (NCT02513303): A Phase 3 US Multicenter Randomized Controlled Trial Evaluating Efficacy of a Perivascularly Delivered Sirolimus Formulation (Sirogen™) for Improving Hemodialysis AVF Outcomes: PCD532. J Amer Soc Neph 32(10S) p 87, October 2021.

Sirogen Demonstrated Improvement for Elderly Patients in an RCT Post Hoc Analysis



Sirogen Denied Due to Failed RCT Primary Endpoint Despite Demonstrated Safety

- Sirogen study demonstrated
  - The device is safe
  - The device results in high functional success
  - RCT failed due to imbalanced randomization
  - Subgroup of elderly patients found to benefit significantly



- Forced to run a new RCT for elderly patients indication despite crossing the safety & probable benefit threshold
- Would it not be *reasonable* to clear Sirogen with an indication for the elderly now?

RCTs In the Hands of FDA Do More Harm Than Good

- Since endoAVF, FDA has delayed market access to safe breakthrough technologies in favor of *unreasonable* assurance of benefit
- Practicing clinicians are the ultimate adjudicators of clinical benefit and data requirements
- Patients and their doctors should be the ultimate deciders in their care
- What do we actually need the FDA to do?
  - Hold companies accountable to manufacturing and biocompatibility standards
  - **Confirm safety** to implant in humans as intended
  - Trust the clinical judgement of clinicians to give the best care to their patients

Prioritize Patient Choice

Patients are the ultimate decision makers, and we must prioritize speed to access to innovative devices with a *probable* clinical benefit

In dialysis access we need better results and better ways to care for this vulnerable population. The FDA's stance on safe devices with probable benefit delays this care and effectively discriminates against a disadvantaged group

Thank You!