Regulatory Approval Of Novel Vascular Access Devices:

When Randomized Clinical Trials (RCTs) are Essential

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Disclosures

- I retired from FDA on September 30
- Any opinions expressed are my own and based on publicly available information
- I have no commercial conflicts

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Widespread Therapies Abandoned After RCTs

Treatment	Proponent
Radical mastectomy for breast cancer	W.S. Halsted
Tannic Acid Treatment of Burns	Roy McClure
Gastric freezing for GI Bleeding	Owen Wangensteen
IMA implantation for angina	Arthur Vineberg
Extracranial-Intracranial Bypass	Y.G. Yasargil / J. Ausman

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Why Randomized Clinical Trials (RCTs) ?

- Randomization helps assure that participants in both treatment groups are similar in the distribution of prognostic factors.
- This minimizes bias in statistical comparisons of patient outcomes when looking at both effectiveness and safety.
- RCTs yield the highest level of evidence to establish causal associations in clinical research, allowing outcome differences to be interpreted as the causal effect of treatment
- No need for statistical slight of hand with propensity scoring or other complex statistical methodology.

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Single Arm Studies

May be beneficial when the range of treatment outcomes for a given condition fall within a narrow range, such as is the case for treating AV graft stenosis with plain PTA

PTA for AV Graft Stenosis

		% Primary Patency	
Author	# Cases	3 months	6 months
Beathard, 1992	536	79	61
Kantermann, 1995	90	N/A	63
Safa, 1996	90	70	47
Turmal-Rodriguez, 2001	98	85	53
Lilly, 2001	330	71	51
Maya, 2004	155	79	51

Hemodialysis vascular access monitoring: current concepts . M Allon & ML Robbin, Hemodial Int, 2009; 13(2) 153-162.

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Major Challenges Using Performance Goals

- **SELECTION BIAS**: Trial subjects are often screened for entry by US, and so likely have better anatomy than those treated in historical reports
- **HISTORICAL BIAS**: Real world results from access creation were driven down by the "Fistula First" initiative
- **STATISTICAL LIMITS**: Without controls, comparison to a PG cannot demonstrate superiority or non inferiority, they can only be met

"It is not generally recommended that a PG originate with a sponsor or be developed unilaterally by FDA for a particular submission."

2013: FDA Guidance Document:
Design Considerations for Pivotal Clinical Investigations for Medical Devices

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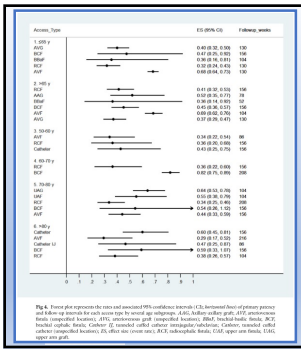

Why a Single Arm Study is Challenging in Dialysis Patients

- When the range of access creation outcomes is broad, defining a meaningful performance goal is a challenge.
- A head to head comparison in a RCT is more apt to make things clear.

Outcomes of vascular access for hemodialysis: A systematic review and meta-analysis. J Almasri et. al. J Vasc Surg 2016:https://doi.org/10.1016/j.jvs.2016.01.053

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Factors Impacting AVF Patency

NONMODIFIABLE	MODIFIABLE
Age	Smoking
Sex	BMI >30
Diabetes	Dyslipedemias
PVD	Antithrombotic Therapy
Cardiac Disease	Anastomotic Technique
Hypotension	Early Creation
Arterial Diameter	Timing of 1st Cannulation
Venous Diameter	Cannulation Technique
Venous Distensibility	Surveillance Intensity

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VasQ Pivotal Study

- Performance goal was 55%;
- PG crafted from 5 papers published between 2007-2011
- Single arm study enrolling 144 subjects at 16 US Centers
- Inclusion criteria minimum sizes: 2.0 mm artery and 2.5 mm vein
- 90% = brachiocephalic AVFs, 10% = radiocephalic AVFs
- 129 BC-AVFs = primary analysis cohort
- Mean BC-AVF vessel diameters:
  - Artery = 4.4 mm (2.5-6.6mm)
  - Vein = 4.0 mm (2.5-7.8mm
- 6-month Primary Patency of 66%

VasQ U.S. pivotal study demonstrates the safety and effectiveness of an external vascular support for arteriovenous fistula creation. ED Dillavou et al. Journal of Vascular Surgery 2023, Volume 78, Issue 5, 1302 - 1312.e3

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Is the Vas Q Device Effective???

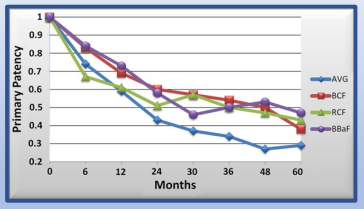
Primary Patency for BC-AVF

Almasri Systematic Review

- **6-month = 80%**
- **12-month = 70%.**

VasQ Pivotal Study:

- **6-month = 66%**
- **12-month = 48%**



Outcomes of vascular access for hemodialysis: A systematic review and meta-analysis. J Almasri et al, J Vasc Surg 2016: https://doi.org/10.1016/j.jvs.2016.01.053

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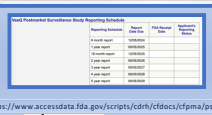
VasQ 522 Mandated Randomized PAS



https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pss.cfm

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Conclusions

- Single arm studies with performance goals are fraught with confounding due to historical, selection, and investigator bias.
- Randomization is essential to minimize the plethora of both the known & unknown factors affecting AV access outcomes.
- RCTs provide the highest level of evidence, allowing observed outcome differences to be interpreted as the causal effect of treatment.

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Conclusions

- Drawing causal inferences from nonrandomized, observational studies is inherently speculative
- RCT's reassure patients, physicians, and payors that new device therapies can be adopted based on robust unconfounded clinical data.
- Doesn't treatment of our vulnerable dialysis patients deserve to be supported by the highest level of clinical evidence. possible?

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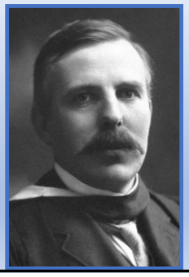
Ernest Rutherford: 1908 Nobel Laureate



" An alleged scientific discovery has no merit unless it can be explained to a barmaid."

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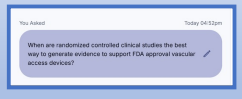
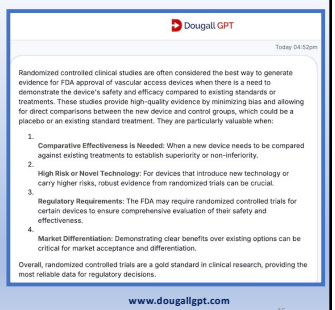
What Does Artificial Intelligence Say About RCT for Regulatory Approval?





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Rebuttal

- Drawing causal inferences from nonrandomized, observational studies is inherently speculative
- Treatment of our vulnerable dialysis patients deserves to be supported by the highest level of clinical evidence available, randomized prospective clinical trials
- Don't you want to be certain that whatever you offer your patients is clearly the best solution for their access??

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