2018 VASA: VASCULAR ACCESS FOR HEMODIALYSIS SYMPOSIUM

How CROs Can Accelerate Approvals for Drugs & Devices for Dialysis Patients

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Disclosures: None

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Patient Perspective has been used in FDA Advisory Committees since 1991→ now its mandated by the 21st Century Cures Act of Dec 2017:

- FDA Patient network
- FDA Patient Representative Program
- FDA Safety and Innovation Act
- FDA and EMA Patient Engagement Cluster
- Patient Engagement Collaborative
- Patient Reported Outcomes
- Patient Focused Drug Development Initiative
- Device Patient Preference Initiative
- Patient Engagement Advisory Committee

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

*2009 Guidance (released in 2011): supports how **PROs as endpoints** in trial can enrich the approval process*

- **PRO Measures in CKD** for :

1. **FSGS**: Mathias et al, 2017
2. **Vascular Access**: Proposed KHI Project (current)
3. **IgAN** from CureGN

- Planned CKD Patient Focused Meetings (NKF)

https://www.fda.gov/ForPatients/PatientEngagement/default.htm accessed on 7April 2018

Patient Engagement Beyond Trial Enrollment

Talk to Dialysis Patients!

Patient Insight Impacts Drug Development & Regulatory Decision Making

- ROI: $100k spent on patient feedback can shorten time to launch with ENPV rise of $75MM (Ph3)
- Obesity Device Approval based on Patient Survey after Primary EP failed (2015)
- "Patient Preference" Data added as a new section to drug label (2017)

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PatientEngagementAdvisoryCommittee/UCM580185.pdf, accessed on 26Oct2017: first Patient Engagement Advisory Committee Meeting

Levitan, Getz, et al, Ther Innov Reg Science 2017; FDA news release Jan 2015; Ho et al, Surgical Endoscopy 2015
https://www.biocentury.com/biocentury/regulation/2017-12-22/how-rituxan-hycela-became-first-drug-patient-preference-data-its-
https://www.gene.com/medical-professionals/medicines/rituxan-hycela, Accessed on 25 Mar 2018

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Protocol Design & Development:

Talk to Nephrologists at CROs…and HD nurses & Techs
So we can ensure the protocol aligns with real life Dialysis care

Protocol section	Avoid this	Example	Challenge	Solution
Endpoints	**Confounders** to Measured Outcome	**Line Reversal** in a Catheter Function Trial	Recirculation decreases Kt/V and Line Reversal may represent Treatment Failure	Refine EP to address outcome in the setting of Line Reversal Call out Line Reversal on CRF
Eligibility Criteria	Too many **unnecessary criteria**	**Urine drug screen** or **Coagulation Panel**	Oliguric or anuric patients Heparinized lines	Evaluate necessity Draw prior to heparinizing lines
Schedule of Assessments & Procedures	**unrealistic data collection that's not consistent with HD care**	**1 or 2 peripheral blood culture draws** *OR* **PI** assess patient **3x/week** *OR* EKGs required **pre-HD or on Sat** *OR assessments* **that prolongs chair time (cath lock)**	Can't access peripheral vein in 40% HD patients [1] Reality is PI rounds at their discretion (1, 2-3 or 4x/mo) 1st shift can start as early as 530a	Specify realistic frequency, necessity, and timing of procedures
Safety	**Assuming regular HD symptoms are AEs**	Recording **cramping/nausea as AEs**	AE overload, introduces noise into data, Site fatigue, query rates are already high	Specify regular symptoms in PMH, only record as AE if worse than usual Specify AEs of special interest relative to IP or EPs

[1]Pelletier et al, CJASN 2016

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Simplify Data Collection…*imperative in HD trials*

Complexity rises with the "wouldn't it be nice to know" analyses

Increasing Complexity of a Typical Phase 3 Clinica Trial.*			
Trial Design Characteristics	**2002**	**2012**	
Total no. of end points	7	13	**Rise: nearly doubled**
Total no. of procedures	106	167	**58%**
Total no. of eligibility criteria	31	50	**61%**
Total no. of countries	11	34	
Total no. of investigative sites	124	196	
Total no. of patients undergoing randomization	729	597	
Total no. of data points collected	NA	929,203	

Rosenblatt, NEJM 2017

Complexity drives up monitoring scope & Cost

- **Procedures account for 20% of trial costs[1]**
- **33% of procedures are related to non-core data (Ph3): do not support primary or secondary EP…yet account for 35% of direct costs[3]**
- **Unused collected data may be 30% of the data, adding $20-35 MM in costs[2]**

Califf, R.M. 2009. ACS and Acute Heart Failure Models. Speaker presentation at the Instiitute of Medicine Workshop on Ttansforming Clinical Research in the United States, October 7-8, 2009, Washington, DC.

[1]Sertkaya et al, 2016; [2] Getz et al, 2010; [3]Tufts CSDD Nov 2012

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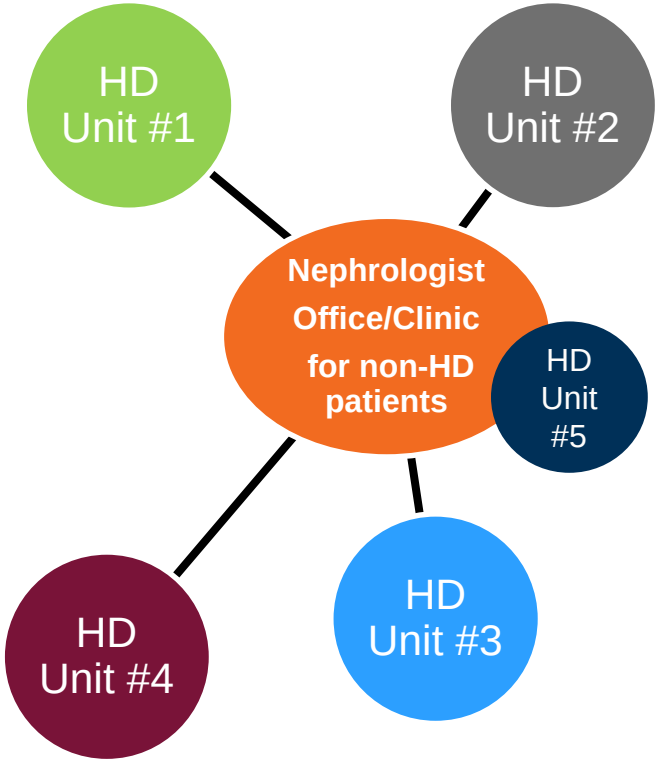
Feasibility based on input from Study Coordinator & Charge RN



Key considerations:

- **Select unit** that's most appropriate for each study (patient population, staff flexibility, etc)
- **IP and study equipment** (e.g. EKG machines)
  - Where will they be shipped to? stored?
  - Unusual requirements for storage? Limiting access to unit staff?
- Where will **source docs** live?
- CRAs: understand **travel time** (between units) & time at each one
- **Contracting** with Dialysis Provider of each study site

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Start Up to Database Lock

Our common goal is speed & pristine data integrity

Start up Activities

- **Work transparently with Dialysis Organizations** to decrease contract & budget times (shorten time from avg of 8 months[1])
- **CROs are reportedly 6 and 11 weeks faster** than sponsors at completing site initiation (for old and new sites)[1]

[1] Tufts CSDD Impact Report March 2018

Recruitment*

- Nephrology **PI must offer, explain, inspire**
- Pre-identification with **centralized data** on access type, lab criteria→ engage Charge RN & Techs
- **Blankets, staff t-shirts, buttons, vidoes (95% have TVs at chair** with study logo prompt trial chatter
- **60% HD pts use the internet**
- **Culture changes** evolve over time (KHI, PCORI, NKF efforts): Trial Participation as a care Option for Care

Data Capture

- Early education of sites & **better worded queries** to decrease high query rates (e.g. SAEs)
- **Simplify CRFs:** HD-associated symptoms are not AEs
- **Thoughtful Con Med data**: don't need every prn & heparin tweak in most trials

***Covance/LabCorp offers "Opt In" to trial participation**

and

Our Xcellerate Knowledgebase™ captures information from Covance Central Labs Service

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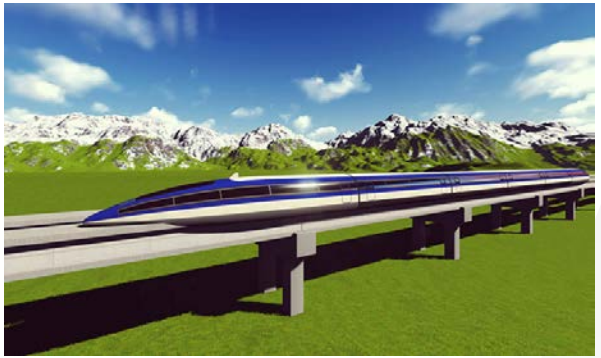
Build on the momentum

Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy

*Adeera Levin†, Marcello Tonelli†, Joseph Bonventre, Josef Coresh, Jo-Ann Donner, Agnes B Fogo, Caroline S Fox, Ron T Gansevoort, Hiddo J L Heerspink, Meg Jardine, Bertram Kasiske, Anna Köttgen, Matthias Kretzler, Andrew S Levey, Valerie A Luyckx, Ravindra Mehta, Orson Moe, Gregorio Obrador, Neesh Pannu, Chirag R Parikh, Vlado Perkovic, Carol Pollock, Peter Stenvinkel, Katherine R Tuttle, David C Wheeler, Kai-Uwe Eckardt†, on behalf of the ISN Global Kidney Health Summit participants**



Levin et al, Lancet 2017 (based on ISN's CKD Summit in July 2016)

Table 9: Theme 9, develop novel therapeutic interventions to slow CKD progression and reduce CKD complications

Table 10: Theme 10, increase the quantity and quality of clinical trials in CKD

"As a stretch goal for the community, we propose that 30% of patients with CKD should be involved in relevant clinical trials by 2030."

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