

Hemodiafiltration Struggles in the US

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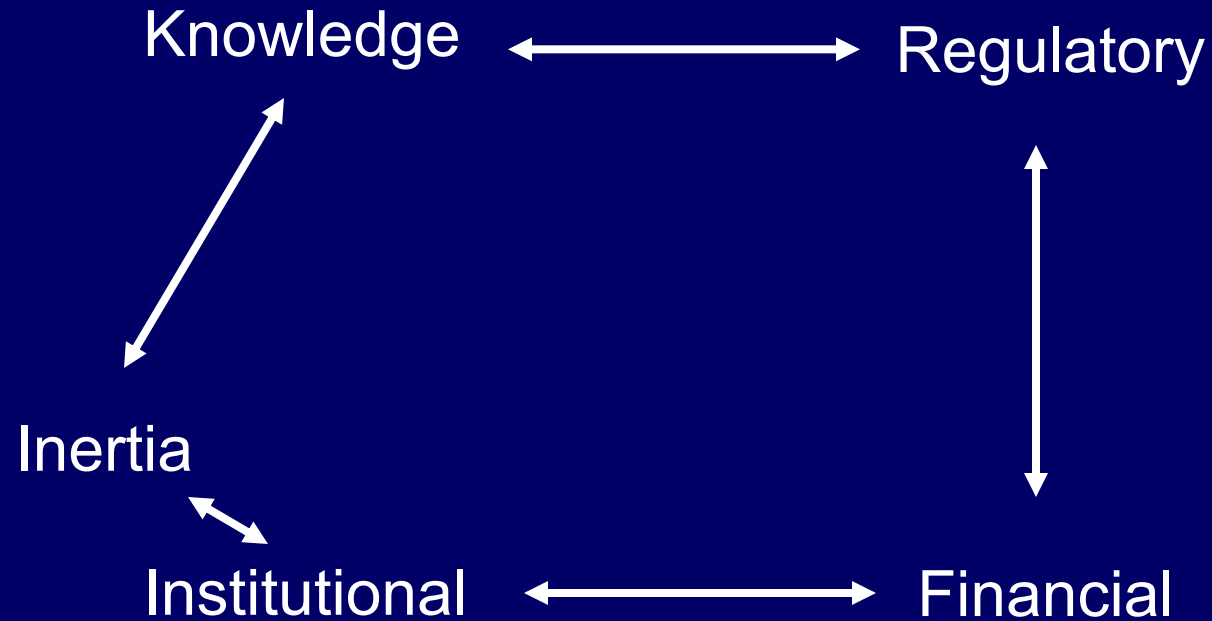
Potential Conflict of Interest Disclosures:

Advisory Boards: CVS Renal, NxStage, LightLine Medical

Royalties: *Up To Date*

Honoraria: Home Dialysis University

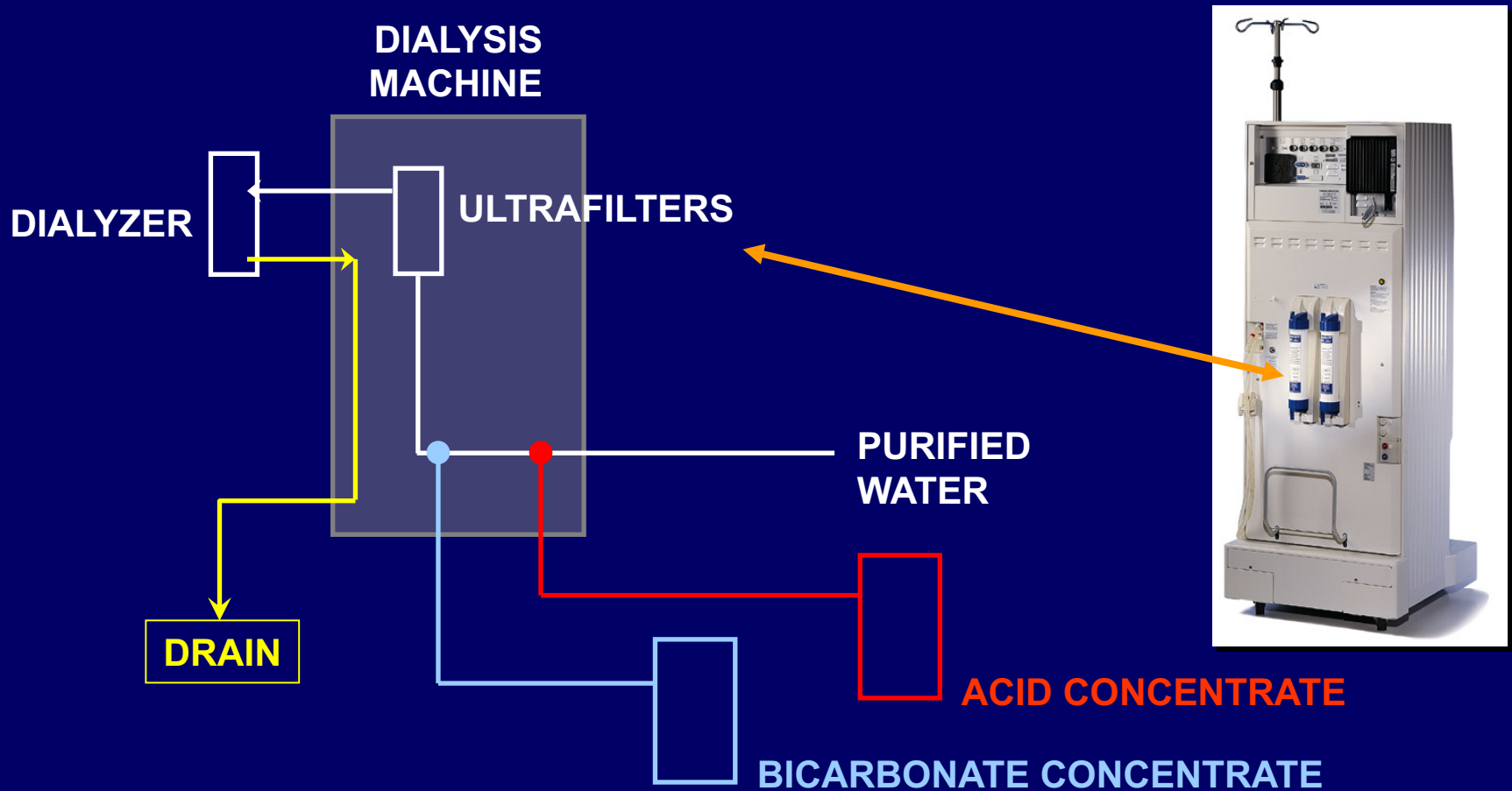
Barriers to HDF in US 2023



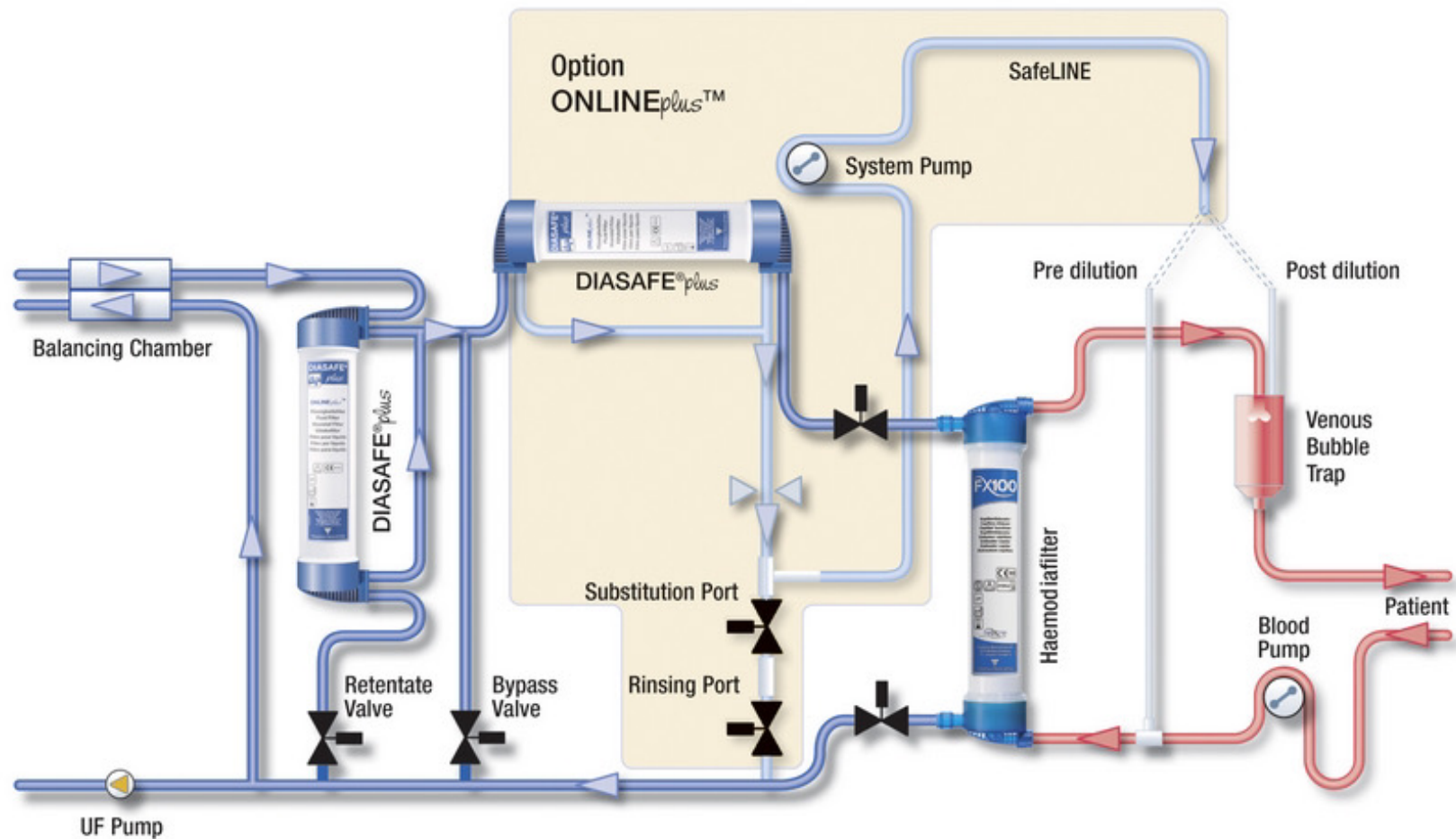
Subtle History 1

- In the late 80s and early 90s outcomes of American dialysis patients were inferior to those in Europe and Japan
 - Americans (myself included) attributed this to patient selection (co-morbidities)
 - Some credence to that
 - Ignored the quality of water and its potential contribution to chronic inflammation and mortality
- In 1992 I visited Montpelier France (Mion, Canaud) and recognized efforts to improve water quality
- Efforts to clean up water for dialysis in US started to take hold
- Diasafe™ filters became routine to improve dialysate water quality

Point-Of-Use Ultrafiltration For Preparation Of Ultrapure Dialysate (about 2000)



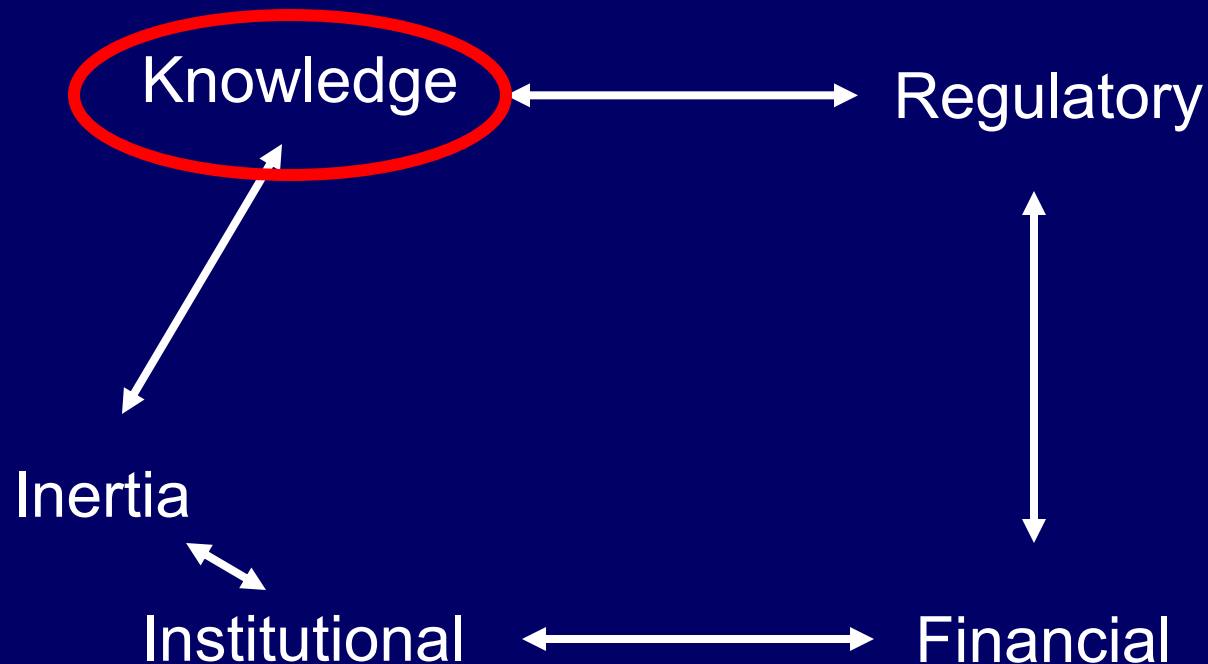
On-line Production of Substitution Fluid: An Extension of Diasafe™



Subtle History 2

- Norman Stockbridge PhD (FDA) and Emil Paganini MD (Cleveland Clinic) hosted an NIH-FDA in 2004 conference on dialysis water purity and sterilization.
 - No opinions were changed
- Nathan Levine and I hired McDermott, Will and Emery to challenge some FDA policy on water sterilization
- We transferred the claim to Fresenius
- Simultaneously, Gambro was working with FDA on dialysis water sterilization processes
 - Both initiatives were inconclusive
- NxStage water processing came the closest to our goal
- 5/13/22 FDA approval for Nephros™ HDF system
 - Used at Vanderbilt for 6 months, abandoned due to complexity, not medical problems

Barriers to HDF in US 2023



CONVINCE

Benefits and harms of high-dose HDF versus high-flux HD

Blankestijn PJ, et al. BMJ Open 2020;10:e033228.

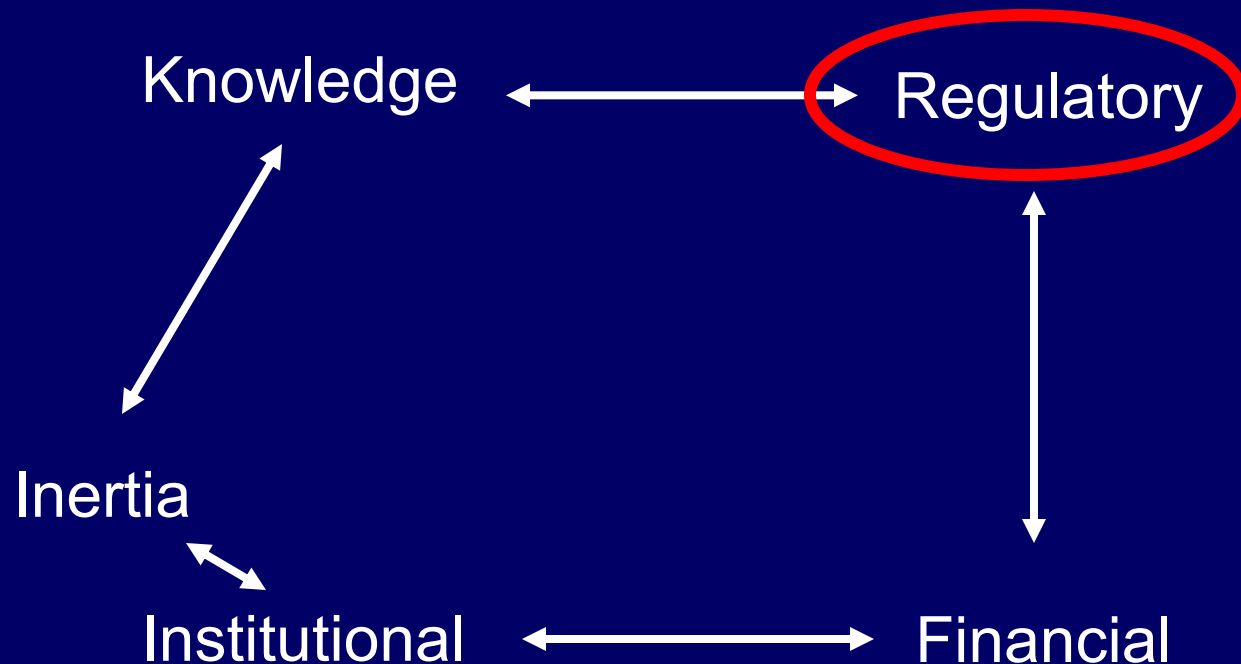
doi:10.1136/bmjopen-2019-033228

- Peter J Blankestijn, Kathrin I Fischer,² Claudia Barth, Krister Cromm , **Bernard Canaud**, **Andrew Davenport**, Diederick E Grobbee, Jörgen Hegbrant, Kit C Roes, Matthias Rose, Giovanni FM Strippoli, Robin WM Vernooij , Mark Woodward, G Ardine de Wit, Michiel L Bots
- Methods and analysis This **prospective, open label, RCT**, 1800 ESKD adults treated with HD in nine **European** countries. **Prevalent** patients will be randomized 1:1 to **high-dose HDF versus** continuation of conventional **high-flux HD**. The primary outcome will be **all-cause mortality at 3 years'** follow-up. Secondary outcomes will include cause-specific mortality, cardiovascular events, all-cause and infection-related hospitalizations, patient-reported outcomes (eg, health-related quality of life) and cost effectiveness
- High dose HDF is defined as a **convection volume of ≥ 23 L** (range ± 1 L)

Knowledge

- Physicians
 - CONVINCE Study by end of 2023?
- Staff (nurses, techs, engineers)
- Unit administrators
- Surveyors

Barriers to HDF in US 2023



My Meeting with FDA 2/3/23

- Gema Gonzalez, Glenn Bell, Doug Silverstein
- Water sterilization for HDF and CFPD
- Pathway exists
- FDA is awaiting proposals
- It cannot divulge who those are coming from
- There are probably 3 or more in the works

Regulatory Considerations for HDF in the United States

Ward et al (Silverstein, Canaud) (KHI Workgroup) CJASN 13:1444, 2018

HDF systems will include components beyond an HDF machine and a high-flux hemodialyzer. These **other components**, which could differ between different systems, need to be considered in developing an approach to gaining regulatory approval for an HDF system. For example, the treated water supply system **must be capable of being effectively disinfected** for sterile, nonpyrogenic fluid to be generated.

In that case, the disinfection process would be an integral part of the clearance or approval of an HDF system.

In addition, **accurate control of fluid balance and ultrafiltration** must be shown to protect against fluid overload or depletion.

Finally, the additional pump and tubing for substitution fluid infusion must have appropriate **safety monitors**.

Regulatory

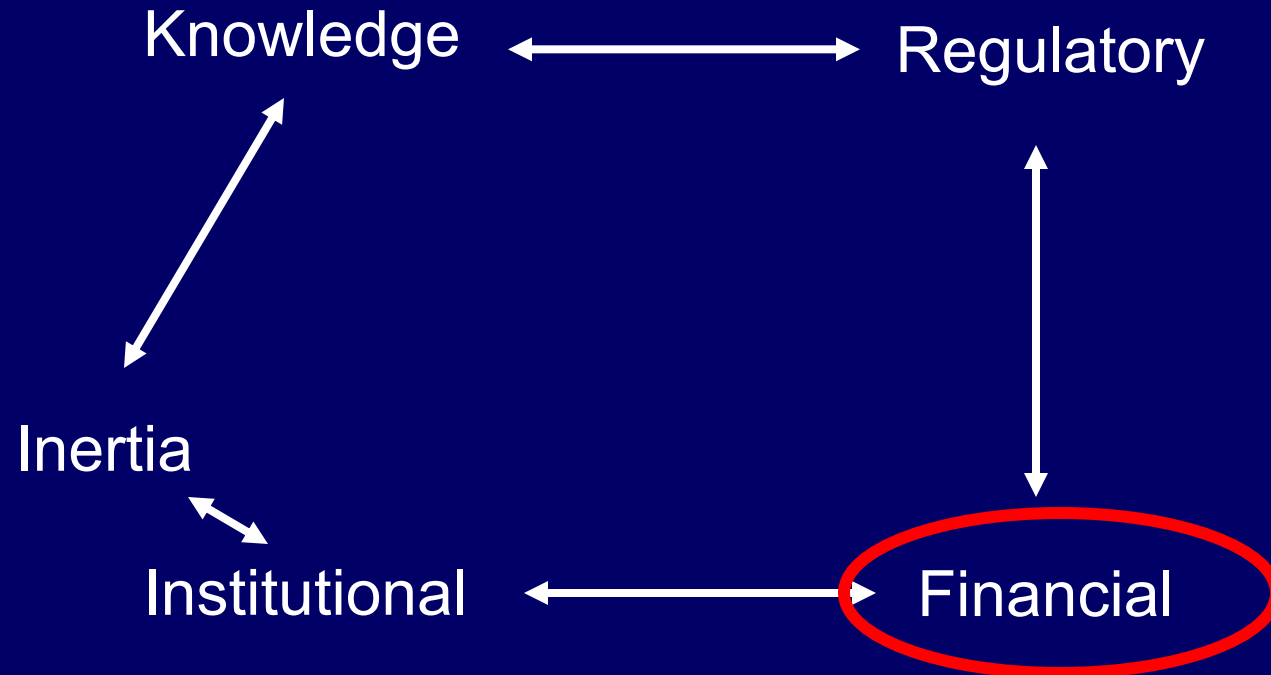
- FDA recognition of filtration as a sterilization process for infused fluids
- Multiple manufacturers in US discussing this with the FDA
- CONVINCE Study by end of 2023?

Regulatory Issues in US

Summary

- Only Nephros™ systems approved now
- At least 3 in preparation and/or assessment
 - Proprietary and choose not to be disclosed
- A pathway for regulatory approval exists
- Online HDF system must be capable of routinely achieving a sterility assurance level of 10^{-6} and nonpyrogenic levels of endotoxin
- Must have redundancy and an appropriate quality management process

Barriers to HDF in US 2023

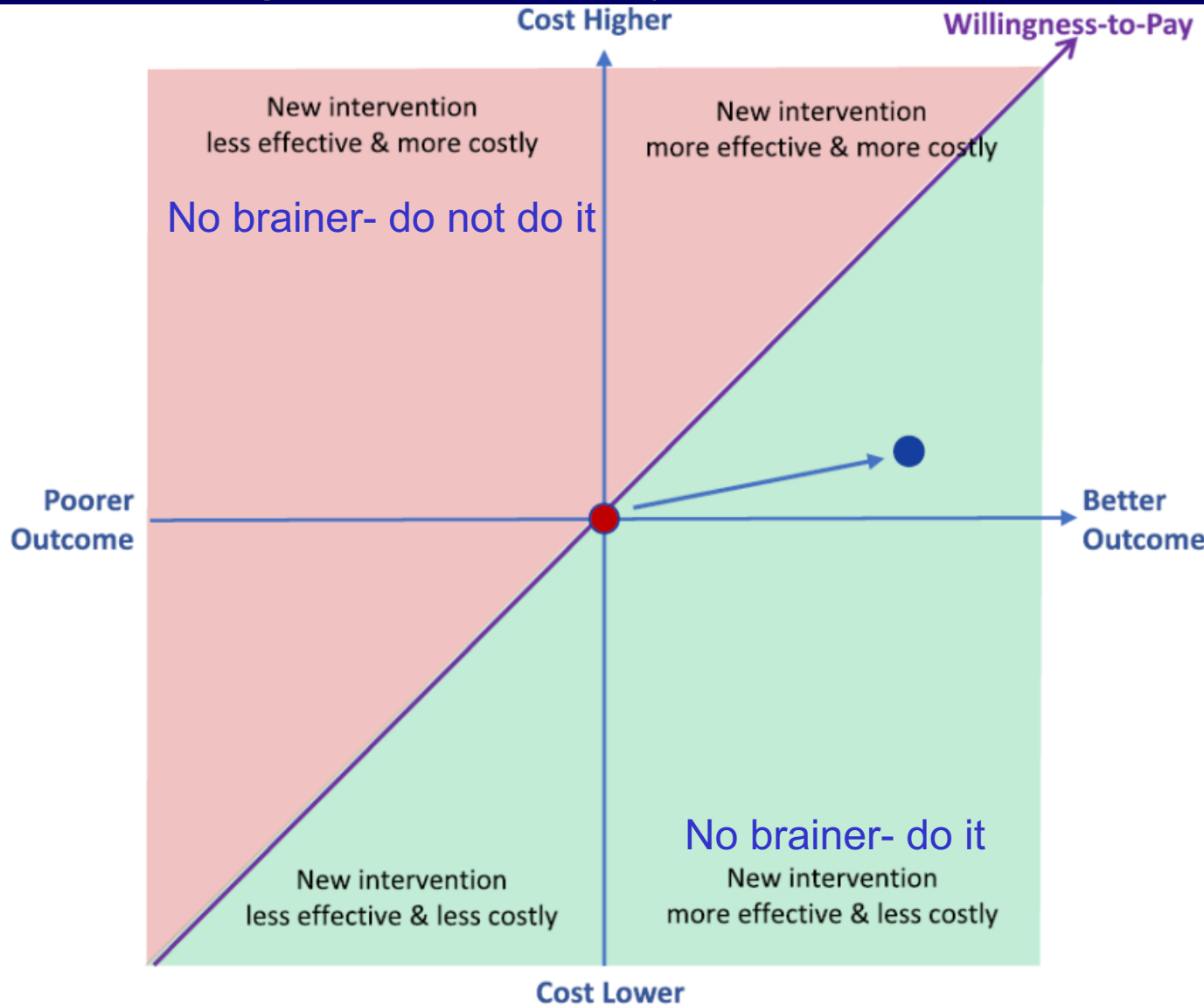


Costs

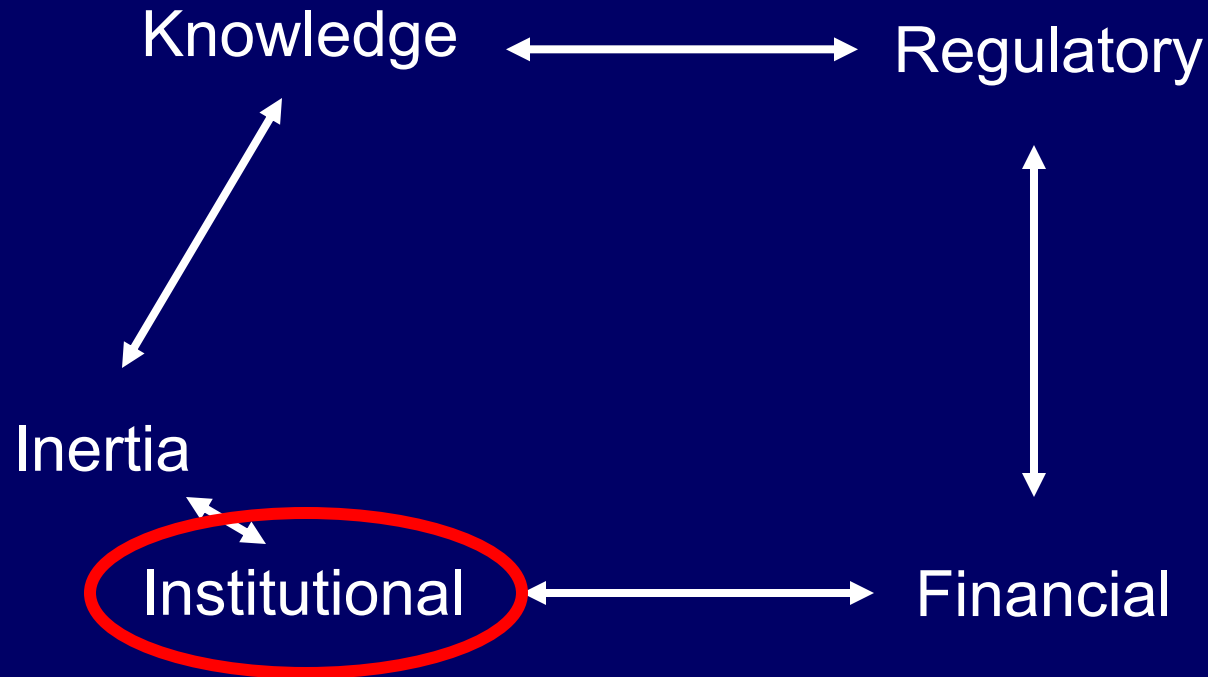
- ESHOL (and others) longer survival, less frequent hospitalizations
 - Maduell F, *et al.* High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *JASN*; **24**: 487, 2013
- Dialysis clinic profits consequently increase
- Hospital expenditures down for payer
- Longer survival costs payer more
- Dialysis clinics must change equipment and modify procedures

What It Probably Comes Down To

Honig et al Sem Dialysis 35:405, 2022



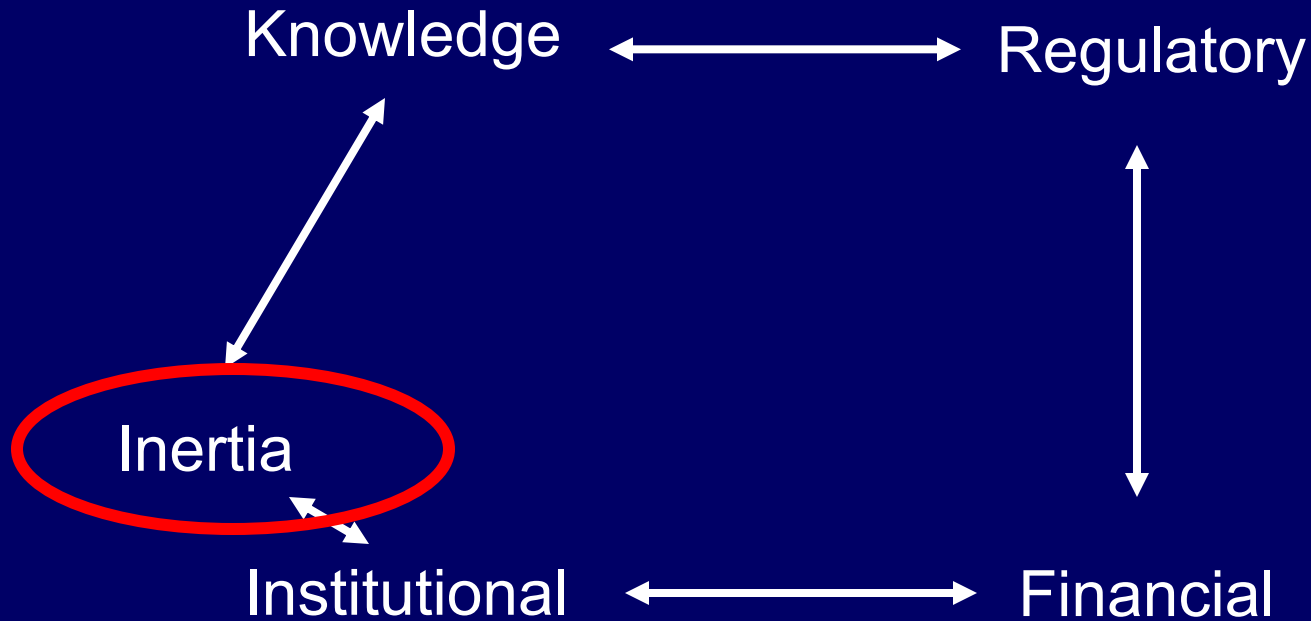
Barriers to HDF in US 2023



Institutions

- Some academic dialysis clinics are interested
- Vertically integrated LDOs may find it best in long run with gradual transition as equipment ages, new clinics open

Barriers to HDF in US 2023



Inertia

- Depend on positive results and patient benefits
- Too few nephrologists and too busy to learn new things
- System disrupters needed but must be done wisely