Clinical Trials

Presenters: E. Wesley Ely, MD, MPH and Pratik Pandharipande, MD, MSCI

Time	Section
03:35	**Focus of today's talk** • Clinical trial design through 2 paths of discovery their program has used
04:15	**Story about use of antipsychotics for treatment of delirium (Ely); path of discovery for alpha 2 agonists for treatment of delirium (Pratik)**

04:49	**Antipsychotics for delirium within the context of the MIND and MIND USA Study**
	• 1970's became usual care, but never subjected to rigorous analysis
	• 2005, developed CAM-ICU, published 2 validation studies
	• Asked the question: "Do antipsychotics work for delirium treatment?"
	  o Need to get enough data to develop a Phase 3 trial
	• Designed a placebo-controlled trial (MIND)→ critical care medicine
	  o Funded by industry
	  o Original: Olanzapine (atypical), Haldol (typical), placebo arm; ended up going with Ziprasidone for the atypical
	• Took pilot data to NIH, applied to NIA for Phase 3 placebo controlled RCT
	  o MIND study (prevention and treatment), NIH restricted to only treatment for MIND USA study
	  o NIA wanted standard of care besides the intervention drug (wanted a protocol across all 3 groups)
	  ▪ Used ABCDEF bundle (non-pharma)
	  o Once bundle implemented, reduced delirium across the board by 25%
	  ▪ Slowed down recruitment/randomization, study lasted 2 years longer than originally planned (got no-cost extensions)
	• Found that antipsychotics didn't do anything for delirium treatment

17:26	**Skipped over in recording: Questions and Answers for part 1 of talk**

17:47	**MENDS studies**
	• How do you come up with study questions? (readings, colleagues, see patients and what's going on and question if what you are doing is the best thing to do)
	  o Study what there is a lot of and seek the truth (have many outcomes)
	• Look into associations between medications we administer to ICU patients and delirium as an outcome
	• First study: look at independent associations of benzodiazepines on outcomes
	  o Found that benzodiazepines administered to ICU patients had higher odds of transitioning to delirium the next day
	  ▪ Is the study question generalizable?, found similar findings in other study populations
	• Once risk factor was identified, led to next question (if particular group of meds are associated with delirium, what is an alternative group of medicines that one should consider?)
	  o Dexmedetomidine→ nobody had studied it for delirium (used for sedation in ICU)
	  ▪ First learn everything you can about the intervention before moving on to interventional trials
	• How to get it into actual practice (look into regulatory issues, funding issues, design issues from the study itself)
	  o Regulatory standpoint: when studying agent for different indication or doses beyond FDA doses it requires contact with the FDA
	  o Funding standpoint: granting agencies are very skeptical until prove you are capable of pulling it off, try to find the best resources (combos of grants), need to have flexibility in thought process of how this will play out
	  o Register protocol and enter changes to track them

	○ Design study issues: confounding variables, changing measurement definitions if needed • Clinical trials take a long time, and often controls get better (improvement in clinical practices) • Blinding in trials (randomize in appropriate manner) ○ Don't want it to affect your science (concerns for patients, concerns for affecting outcomes) • Any clinical trial you do affects how the medical team thinks about treating the patient ○ Have to "babysit" the trial to make sure everything gets done
40:52	**"Babysitting" the study** • Important take home point, babysit every single aspect of the investigation
41:46	**Questions and Answers**