



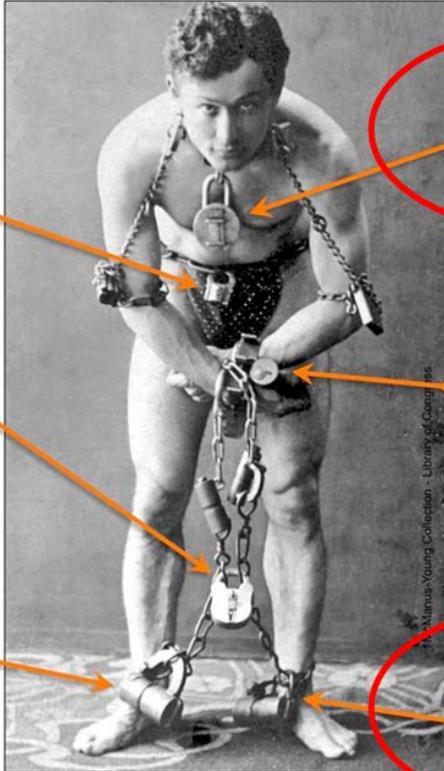
INFLUENZA AND EID THERAPEUTICS

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October, 2016

Roadmap

- Influenza and MERS Co-V

- What is our goal?
- Lineup
- Challenges
- Strategies



Can't do non-inferiority design

Placebo use is unethical

May test dose levels, but don't underdose

Drugs are similar for non-resistant viruses

If resistance to SOC treatment circulates, stop SOC study arm

Endpoint has never been validated

Houdini Clinical Trial

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Courtesy Francisco Marty OPTIONS IX meeting

Program Strategy and Goals - Influenza

Program Goal

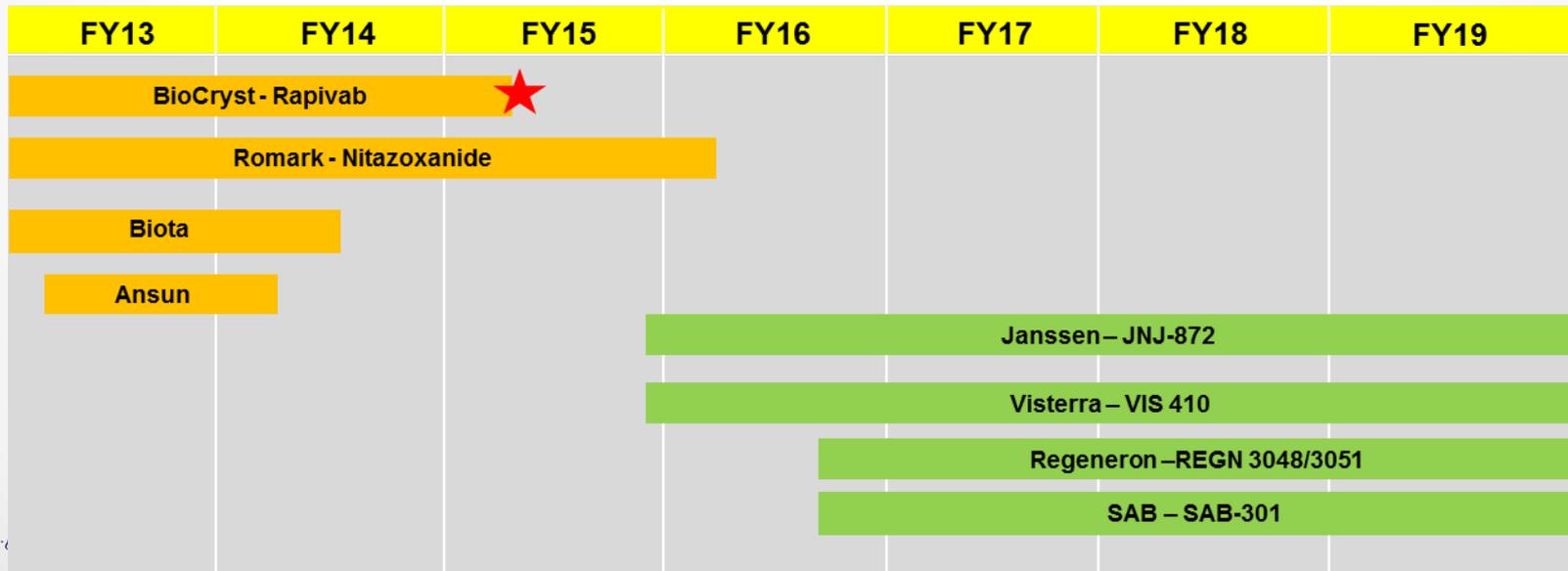
Reduce morbidity and mortality in all patient populations during an influenza pandemic by supporting advanced development, evaluation, and approval of new influenza antiviral drugs

- Mission established in the 2005 *National Strategy for Pandemic Influenza*, *HHS Pandemic Influenza Plan* and the 2006 *Implementation Plan for the National Strategy for Pandemic Influenza*
- Strategy to achieve the goal combines stockpiling existing antiviral drugs with development of new antivirals to address critical unmet medical needs for treating severely ill, hospitalized and pediatric populations



Influenza and MERS CoV

- 4 development programs and 1 task order
 - Janssen – JNJ-872; Phase 3 development program for the hospitalized and high risk influenza infected population
 - Visterra – VIS410 mAb; Phase 2 and 3 development program; hospitalized, high risk, and pediatric influenza infected populations
 - Regeneron – REGN 3048/3051 for MERS infected patients
 - SAB Biotherapeutics – SAB-301 for MERS infected patients



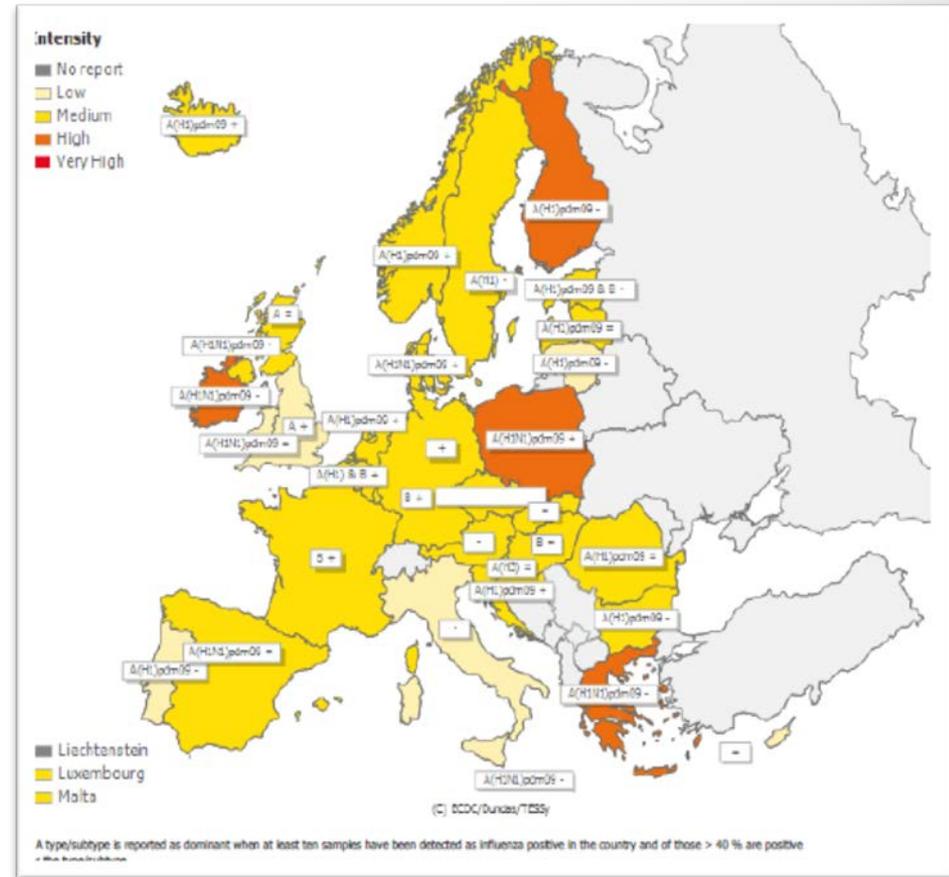
Challenges and Gaps - Influenza

- Influenza therapeutic trial enrollment, execution, and endpoints
- Current gaps in our preparedness:
 - Severely ill, hospitalized influenza patients
 - More effective treatment options, suitable for all populations including pediatrics



Influenza Therapeutic Trials are HARD!

- Seasonal
- Different circulating viruses each year
- Geographic spread is unpredictable



Source: ECDC TESSy reports, week 7 2016, [Europe influenza epidemiology](#)



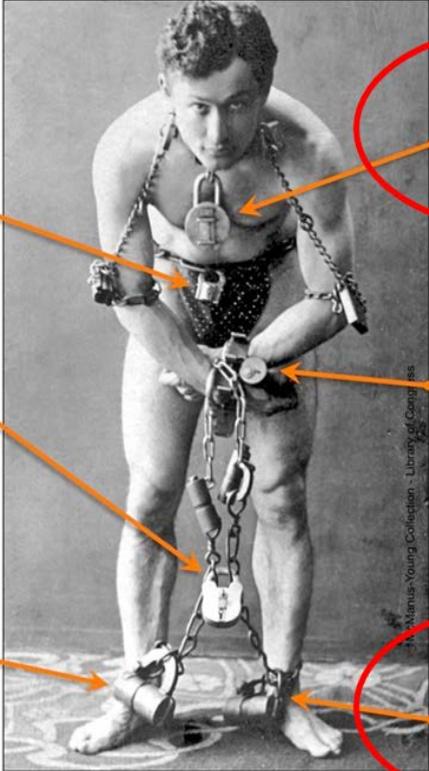
Hospitalized Trials are Harder!

- SOC differs between hospitals and countries
- NAIs are SOC for hospitalized patients yet only approved for acute, uncomplicated illness
- Hospitalized influenza patients are a heterogeneous population
- Clinical study sites enroll on average less than one subject per site per season
- Current clinical endpoints are challenging to measure and demonstrate benefit



Clinical Trial Challenges

- Trial enrollment
- Heterogeneous population
- ENDPOINTS
- Trial design



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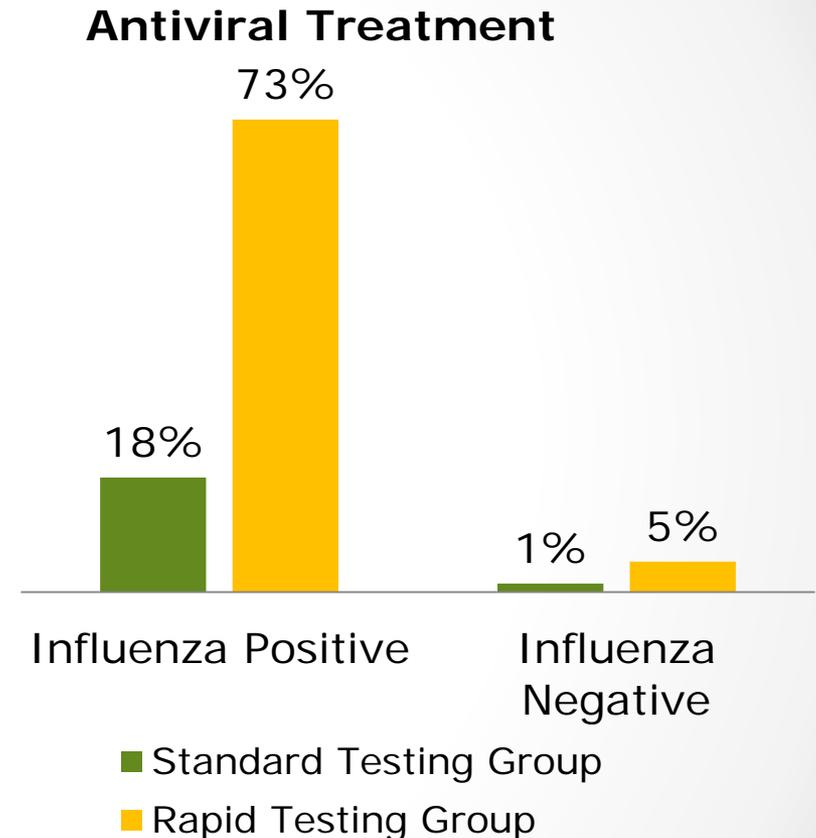
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Houdini Clinical Trial

Courtesy Francisco Marty OPTIONS IX meeting

How Can We Improve Enrollment?

- Rapid diagnostic testing was used to identify and treat influenza subjects while in the Emergency Department
- 2014-2015 season: 1000 flu+ patients identified in 4 EDs



Enrollment Improved!

- 2015-2016 season -
1 ED enrolled 58 subjects
 - 24 hospitalized subjects
 - 34 outpatients



■ Recommendations

- Identify subjects in the ED for early enrollment and treatment
- Include ED clinicians on clinical site contracts
- Find sites that have rapid influenza testing as SOC in the ED resulting in 24/7 coverage



Baseline Severity

National Early Warning Score (NEWS)

- Homogenize the study population based on severity score
- NEWS score > 3 chosen for further analysis



Source: Royal College of Physicians, UK

Observation chart for the National Early Warning Score (NEWS)

NEWS KEY 0 1 2 3		NAME:	D.O.B.	ADMISSION DATE:		
DATE TIME					DATE TIME	
RESP. RATE	≥25			3	≥25	
	21-24			2	21-24	
	12-20			1	12-20	
	9-11			1	9-11	
	≤8			3	≤8	
SpO ₂	≥96			1	≥96	
	94-95			2	94-95	
	92-93			3	92-93	
	≤91			3	≤91	
Inspired O ₂ %	%			2	%	
TEMP	≥39°			2	≥39°	
	38°			1	38°	
	37°			1	37°	
	36°			1	36°	
	≤35°			3	≤35°	
NEW SCORE uses Systolic BP BLOOD PRESSURE	230			3	230	
	220				220	
	210				210	
	200				200	
	190				190	
	180				180	
	170				170	
	160				160	
	150				150	
	140				140	
	130				130	
	120				120	
	110			1	110	
	100			2	100	
	90			3	90	
HEART RATE	>140			3	>140	
	130			2	130	
	120				120	
	110			1	110	
	100				100	
	90				90	
	80				80	
	70				70	
	60				60	
	50			1	50	
	40			3	40	
	30				30	
	Level of Consciousness	Alert V / P / U			3	Alert V / P / U
	BLOOD SUGAR					BI'd Sugar
	TOTAL NEWS SCORE					TOTAL SCORE
Additional Parameters	Pain Score				Pain Score	
	Urine Output Monitoring Frequency Escalation Plan Y/N n/a Initials				Urine Output Monitor Freq Escal Plan Initials	

National Early Warning Score: July 2012

Please see next page for explanatory text about this chart.

© Royal College of Physicians 2012



Current Endpoints

- FDA Guidance for Industry – Influenza: Developing Drugs for Treatment and/or Prophylaxis (2011)
 - Primary Endpoint should include:
 - Clinical signs and symptoms
 - Duration of hospitalization
 - Time to normalization of vital signs
 - Fever
 - Respiratory status
 - Heart rate
 - Systolic blood pressure
 - Supplemental oxygenation requirements
 - “Proposed endpoint [should] directly measure how a patient feels, functions, or survives...”



Clinical Endpoints Working Group

- Government and academic working group
 - WG has looked at therapeutic sponsor, research and hospital databases

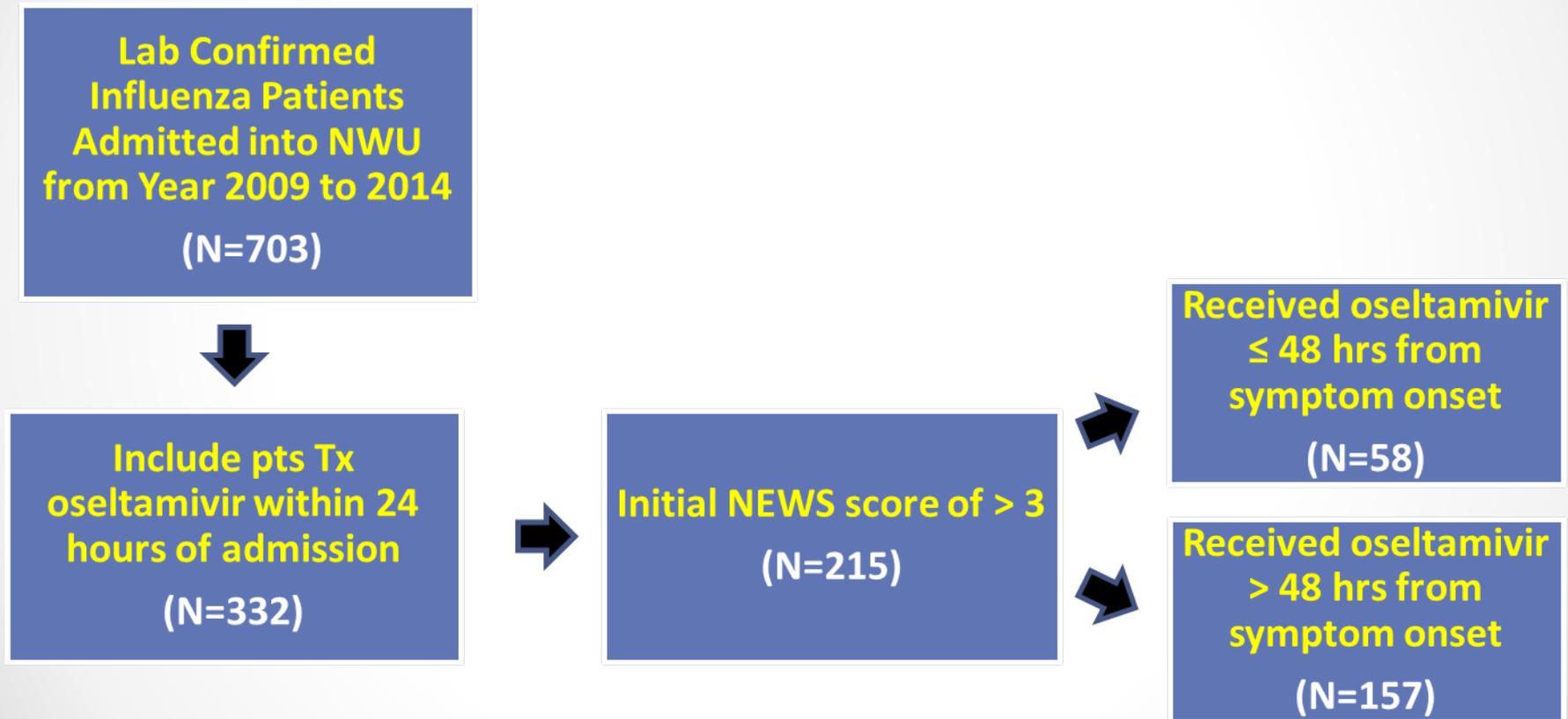
- Ordinal Scale
 - Discrete categories for classifying hospitalized subjects over time could include:
 - Death
 - ICU on mechanical ventilation
 - ICU
 - Hospital floor receiving supplemental oxygen
 - Hospital floor without supplemental oxygen
 - Discharge but has not returned to normal activity
 - Discharge returned to normal activity



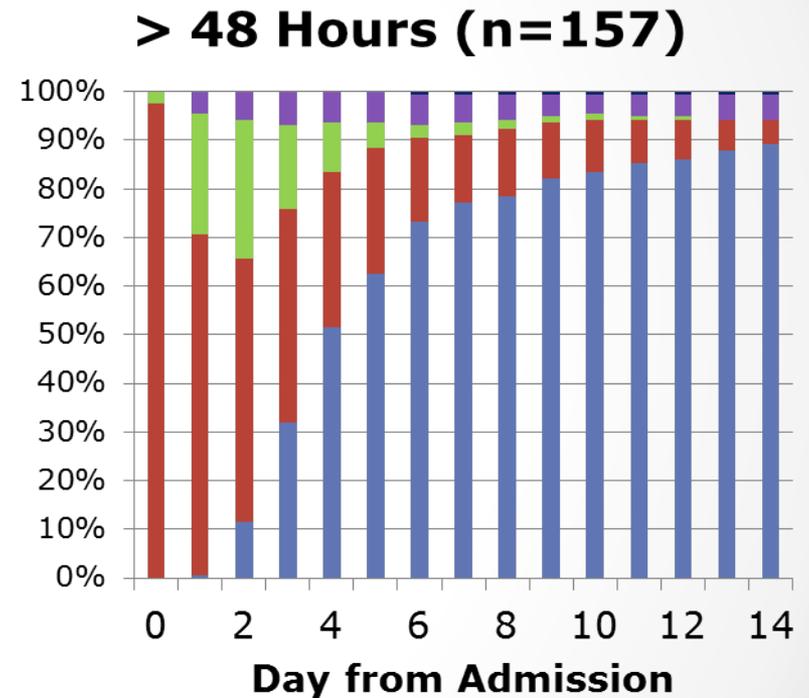
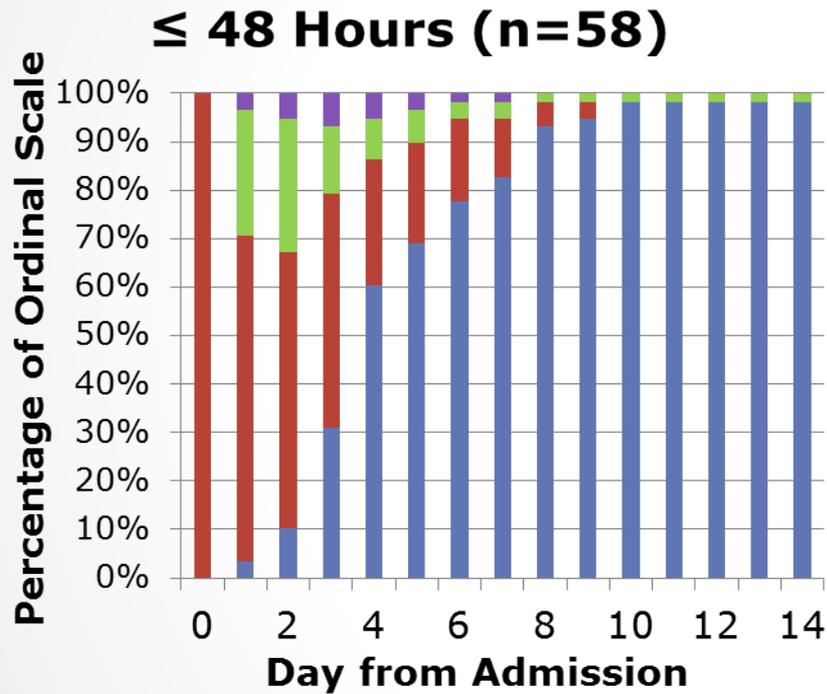
What Does the Data Look Like?

- Retrospective
 - Northwestern University shared data from all flu+ patients 2009-2014
 - With retrospective data, not all classifications are possible
5. Death
 4. ICU on mechanical ventilation
 3. ICU
 - ~~Hospital floor receiving supplemental oxygen~~
 2. Hospital floor ~~without supplemental oxygen~~
 1. Discharge ~~but has not returned to normal activity~~
 - ~~Discharge returned to normal activity~~

Determination of Analysis Population



Frequency Distribution of Ordinal Scale



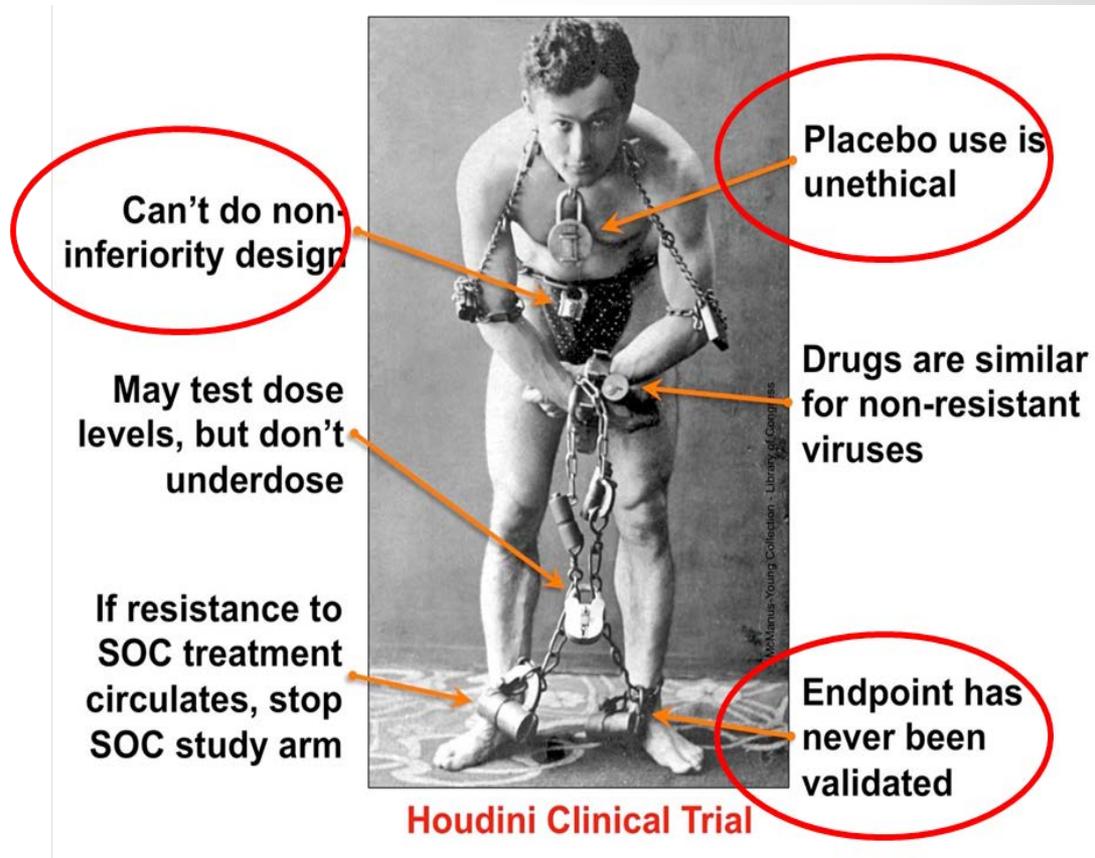
Questions Remain

- What kind and how much data is required to determine if ordinal outcomes are a suitable endpoint for hospitalized influenza studies?
- What is the appropriate statistical measure?
 - Is assigning a number to each category valid?
 - Many possible statistical measures and models, how do we choose?
 - Time to event analysis or reduction in disease burden analysis?
- What is the right balance between disease severity and the ability to enroll a clinical trial?
- **What do the regulators think?**



Clinical Trial Design

- NAIs used off-label as SOC per WHO, CDC, IDSA guidelines to treat hospital patients
- Default design becomes drug + SOC vs SOC alone; but SOC varies

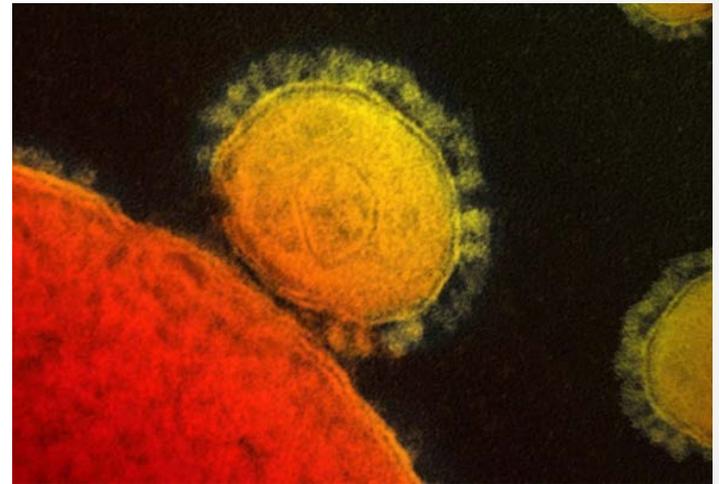


Courtesy Francisco Marty OPTIONS IX meeting

Influenza and MERS CoV

Similarities

- Severe Influenza
 - There are many challenges to developing a therapeutic for the severely, ill hospitalized population.
 - BARDA strategy is to break the challenges up into smaller pieces so that we can address each one
- Why MERS CoV?
 - Severe MERS CoV infection looks clinically very similar to severe influenza infection
 - ~40% case fatality rate
 - BARDA can apply what we know about severe influenza to development of therapeutics for MERS CoV



Program Goals – MERS CoV

Establish the capability to respond to a MERS CoV outbreak with therapeutic MCMs

- Strategy to prioritize MCM
 - Funnel all early stage drugs through the mouse models established at U. Maryland
 - If there is POC efficacy in the mouse, then test the drug in the NHP model established at Rocky Mountain Labs
 - Positive data from the NHP is the trigger for advancement into Phase 1
- Monoclonal mAbs REGN 3048/3051
- Polyclonal abs SAB-301



Trajectory for the Future

- Influenza
 - Continue work towards improvement of trial execution (enrollment, endpoints, design)
 - Diversify portfolio with new MOA drugs
- MERS
 - Continue to monitor landscape and support development of promising candidates
 - Work with interagency partners to define clinical development pathway



Partnership Opportunities with BARDA

- Broad Agency Announcement (BAA)
- We encourage frequent interactions prior to submission



What Types of Data?

- *In vitro* studies demonstrating broad-spectrum neutralizing activity across multiple subtypes of influenza A viruses including but not limited to modern strains of H1N1, H3N2, H5N1 and H7N9
- Pre-clinical animal studies demonstrating efficacy against multiple strains of influenza
- Data to support a wider therapeutic window (48-96 hours after infection with a preference for 72-96 hours after infection)
- Data to support combination therapy with other influenza drugs



Team

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Thank you!





Questions?



Thank you!

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