



# Data Driven Clinical Trial Design

A System for Evaluating Response to  
Therapeutic Interventions

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# Disclosure Information

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# MSG Score System 1980



A system proposed to evaluate therapeutics  
in a variety of fungal infections

\*Dismukes, et. al

# Coccidioidomycosis Epidemic

- 150,000 (>350,000 Infections/Year)
- 60% Asymptomatic
- 40% Symptomatic
- 10% Diagnosed/Treated (largely pulmonary)
- 1% Disseminated (1,500/year)\*
  - 50% Meningeal Disease
  - 50% Non-Meningeal Disease

\*Smith, et. al

# Challenges & Solutions

- Coccidioidomycosis has a complex host parasite relationship
- Severe disease is almost certainly a failure of host defense
- Solutions:
  - New/Better Antifungals
  - Immunomodulators
  - Vaccine

# Mycotic Diseases

- Original MSG was generic
- MSG 1980 unaware of advances to be made
- MSG 1980 did not specifically deal with the variety of non meningeal sites

# Methods

- Literature search for studies using MSG & its many modifications in Coccidioidal Therapeutic Research
  - PubMed, Google Scholar, Research Gate & Embase were searched from 1957 to 2020
  - Multiple Endpoints in Clinical Trials, US FDA 2017
- 
- First, Discuss Multiple End Point Trials
  - Second, Discuss MSG 2020 Cocci

# Research for Drug Approval

- Safety
- Substantial Efficacy



# Efficacy: Phase III Trials

- Avoidance of Type I Error
  - Not a Chance “Win”
- Clinical Importance
  - Death

# Efficacy

- Test of Hypothesis:
  - Null Hypothesis:
    - ✓ No Treatment Effect
  - Alternative Hypothesis:
    - ✓ Positive Treatment Effect

# Efficacy

- Endpoints Designated Prospectively
  - Primary (Single or few)
  - Secondary
  - Exploratory

# Control Prospectively

- End Points
- Time Points
- Population
- Analysis

# Treatment Effect

- Point estimate (time)
- P Value
- Confidence Interval

# Composite Endpoints

- More than one clinical outcome in a clinical trial is important
- All outcomes are expected to be affected by the treatment
- Reasonably similar clinical importance

# Multicomponent Endpoints

- Within patient
  - Two or more components
- Observation of all the specified components (in that patient)
- A single overall rating is determined by specified rules
- Ordered categorical or continuous numeric scales are deemed appropriate

# MSG 1980

## Improving Clinical Relevance

- Parameters that are not necessarily reproducible
  - Temperature\*
  - HA (Severity)

\*Sanctor Sanctorius ~ 1592



# MSG 2020 COCCI

## Result

- Evaluated original MSG Score & subsequent iterations for:
  - Relevant clinical manifestations of diseases
  - Measurable variables that are reproducible particularly in multicenter studies

# MSG 2020 COCCI Result

- Pulmonary & Non-Meningeal (NMD) continue to be considered in the same score system
- Meningeal Disease remains in a separate score system
- Severity is based on clinical parameters, laboratory and radiographic data

# NMD MSG 2020 COCCI

Compatible Clinical Illness & Unequivocal Diagnosis		
<b>General</b>	Weight loss (kg): 10% weight loss at onset of symptoms pre-treatment	1
<b>Laboratory Values</b>	Hypoalbuminemia (<3.5g/dL)	1
	CRP (>10mg/L)	1
	ESR (Male: >22mm/Hr, Female: >29mm/Hr)	1
	Eosinophilia (Abs Eos* >350 cells/uL)	1
<b>Skin Test Negative</b>	Bidirectional < 5mm induration	1

## NMD MSG 2020 COCCI

<b>Pulmonary (6 Points Max)</b>	Room Air: $SPaO_2 < 70$ mm Hg or an A-a $O_2$ gradient $> 35$ mmHg	<b>1</b>
	Room Air: $PaO_2 / FiO_2$ Ratio $\leq 300$ mm Hg	<b>2</b>
	# of Lobes Affected	<b>1/lobe</b>
	Pleural Effusion	<b>1</b>
	Hilar Adenopathy	<b>1</b>
<b>Skin (6 Points Max)</b>	1 <sup>st</sup> Lesion	<b>2</b>
	Subsequent Lesions	<b>1</b>
	Pain	<b>1</b>

# NMD MSG 2020 COCCI

<b>Subcutaneous Abscess (6 Points Max)</b>	1 <sup>st</sup> Lesion	<b>2</b>
	Subsequent Lesions	<b>1</b>
<b>Joints (6 Points Max)</b>	1 <sup>st</sup> Joint Involved	<b>2</b>
	Subsequent Joints Involved	<b>1</b>
	Pain	<b>1</b>
<b>Bone (6 Points Max)</b>	1 <sup>st</sup> Lesion	<b>2</b>
	Subsequent Lesions	<b>1</b>
	% Destruction:> 50% (MRI or CT Imaging Required)	<b>1</b>
	Pain	<b>1</b>

# NMD MSG 2020 COCCI

<b>Intra-Abdominal</b>	Diagnosis	1
	Abdominal Pain	1
<b>Lymph Nodes</b> Palpable or Mediastinal >1 cm on CT	1 <sup>st</sup> Lesion	2
	Subsequent Lesions	1
	Mediastinal Adenopathy	1
<b>Other Sites of Dissemination</b>	NMD Sites of Dissemination not Listed	1
	If Meningeal, Defer to Meningeal Score System	

# NMD MSG 2020 COCCI

Complement Fixation Titers	1:4	0
	1:8 - 1:16	1
	1:32 - 1:64	2
	1:128	3
	>1:128	4
Diagnostic Criteria	Antigen Detection CM (+)	1
	Culture CM (+)	1
	Histopathology CM (+)	1
Total MSG 2020 Score		

## NMD MSG 2020 COCCI

Non-Meningeal Disease MSG 2020 Score Reduction (%)	
Responders	>50%
Partial Responders	30 - 49%
Non-Responders	<30%
Progressors	Initial Score Increased



**MD**  
**MSG 2020**  
**COCCI**

<b>Headache</b>	Yes	<b>1</b>
<b>Level of Consciousness</b>		
	Awake, Alert, Oriented	<b>0</b>
	Cloudy/Delirium	<b>1</b>
	Obtundation/Stupor	<b>2</b>
	Coma	<b>3</b>
<b>New Focal Neurologic Deficits</b>		
		<b>2</b>
<b>Intracranial Pressure (mm H<sub>2</sub>O)</b>		
	<200	<b>0</b>
	200 - 250	<b>1</b>
	251 - 450	<b>2</b>
	>450	<b>3</b>
<b>Neuroradiology</b>		
	Basilar Leptomeningeal Enhancement	<b>1</b>
	Hydrocephalus	<b>1</b>
	Vasculitic Infarction	<b>1</b>
	Mass Lesion	<b>1</b>
<b>Total</b>		

# MD MSG 2020 COCCI

CSF WBC	<20/mm <sup>3</sup>	0
	21 - 100/mm <sup>3</sup>	1
	≥101/mm <sup>3</sup>	2
CSF Glucose (mg/dL)	>40	0
	20 - 39	1
	<19	3
CSF Protein (mg/dL)	≤100	0
	≥101	1
CSF Complement Fixation Titers	Nonreactive	0
	1:1 - 1:2	1
	1:4 - 1:8	2
	≥1:16	3
Culture C. Immitis	Negative	0
	Positive	3
Total		

## MD MSG 2020 COCCI

Meningeal Disease MSG 2020 Score Reduction (%)	
Responders	>40%
Partial Responders	20 - 39%
Non-Responders	<20%
Progressors	Initial Score Increased

# MD MSG 2020 COCCI

Finally, we have added PRO/HQL to patient evaluations

- SF 12v2
- SF – 36
- EQ-5D-5L
- PROMIS Global 10

# Conclusion

We have endeavored to develop a more complete and objective system of evaluations with parameters that are clinically available and reproducible

*“We hope the spirit of these remarks will spark lively discussion as well as constructive criticism, challenge, and controversy ... if indeed such healthy discussion, argument, and dialogue ensues, then we will have satisfactorily accomplished our goal.”*

*- Dismukes et. al*

# Questions?

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