ECMM/MSGERC MYCOLOGY CLINICAL TRIAL RESPONSE CRITERIA

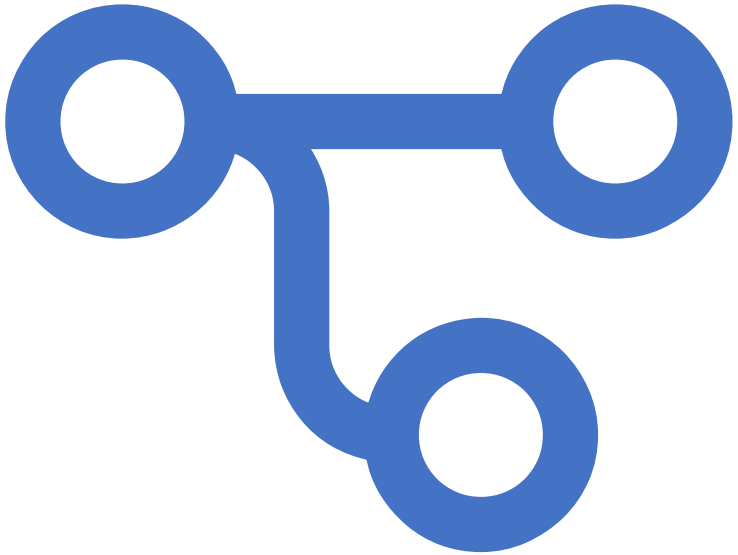
Collaborative Working Group of the ECMM & MSGERC

Listening Session

8 January 2024 8-9:30 AM Central Time US

Roadmap for Today's Listening Session

- Introduce project purpose and structure
- Brief review of 2008 Criteria (Segal et al, 2008)
- Listening session



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Collaborative Project Purpose

- Redefine clinical mycology response criteria for clinical trials and clinical treatment

WHY IS THIS IMPORTANT TODAY?

Outdated success criteria, requires new lens

Lack innovation: current diagnostics, "Real World" approaches, new study methodologies

Lack of patient important outcomes, patient input

Set the stage for DOOR criteria

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General Response Criteria

Segal et al 2008
Clin Infect Dis 47(5): 674-683
doi: 10.1086/590566

OUTCOME, RESPONSE	CRITERIA
SUCCESS	
Complete Response	Survival within the prespecified period of observation, resolution of all attributable S/S of disease and radiologic abnormalities, and mycological evidence of eradication of disease
Partial Response	Survival within the prespecified period of observation, improvement of attributable S/S of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden, as assessed by a quantitative and validated laboratory marker.
FAILURE	
Stable Response*	Survival within the prespecified period of observation and minor or no improvement in fungal disease, but no evidence of progression, as determined based on a composite clinical, radiological and mycological criterion.
Progression of fungal disease	Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria.
Death	Death during the prespecified period of evaluation, regardless of attribution.

**In certain invasive fungal disease (e.g., invasive mold disease), stabilization of fungal disease during periods of severe immunocompromise provides evidence of efficacy of treatment and may be a reasonable short-term therapeutic goal until immune recovery occurs.*

Invasive Mold Disease as an example

Segal, et al, 2008

OUTCOME, RESPONSE	CRITERIA
SUCCESS	
Complete response	• Survival and resolution of all attributed S/S of disease; PLUS • Resolution of radiological lesion(s); persistence of only a scar or post-operative changes can be equated with a complete radiological response; PLUS • Documented clearance of infected sites that are accessible to repeated sampling (e.g., mold disease involving the palate, sinuses, or cutaneous lesions
Partial response	• Survival and improvement of attributable S/S of disease; PLUS • At least 25% reduction in diameter of radiological lesion(s); PLUS • Documented clearance of infected sites that are accessible to repeated sampling (e.g., mold disease involving the palate, sinuses, or cutaneous lesions • In cases of radiological stabilization (defined as 0% -25% reduction in the diameter of the lesion), resolution of all attributable S/S of fungal disease can be equated with partial response. • In cases of radiological stabilization, biopsy of an infected site (e.g., lung biopsy) showing no evidence of hyphae and negative culture results can be equated with a partial response.
FAILURE	
Stable response	• Survival and minor or no improvement in attributable S/S of disease; PLUS • Radiological stabilization (defined as 0% - 25% reduction in diameter of lesions); OR • Persistent isolation of mold or histological presence of invasive hyphae in infected sites
Progression of Disease	• Worsening clinical symptoms or signs of disease; PLUS • New sites of disease or radiological worsening of preexisting lesions; OR • Persistent isolation of mold species from infected sites
Death	• Death during the prespecified period of evaluation regardless of attribution

Minimum period of observation is at least 6 weeks for primary therapy trials; 12 weeks for secondary endpoints. Salvage therapy: 12 weeks after enrollment.

Clear evidence of a radiologic response (reduction in diameter by at least 25% with no new sites of disease) should be given more weight than subjective nonspecific or difficult to quantify S/S of disease. In fungal pneumonia- radiological improvement with persistent cough = partial response. Because radiological improvement often lags behind clinical improvement, especially if a short-term period of evaluation is employed (See Invasive Asp/Other Molds), suggested that radiological stabilization and resolution of attributable S/S = partial response. Serum galactomannan index is a promising correlate of therapeutic outcome.

Issues in Aspergillus/Other Molds Outcomes

- Stable = Failure
  - Is this true for primary and salvage therapy? Is this true for all mold pathogens?
- Death = Failure
  - Is this true for non fungal infection related death?
- Radiological response trumps clinical response for Global assessment
  - What is really important for the patient?
- We are in 2024 not, 2008
  - Implement novel radiologic (PET/functional imaging) and microbiologic tests (GM, PCR, others) into response criteria?

Collaborative Leadership Structure

Executive Committee

MSGERC	ECMM
Luis Ostrosky	Neil Gow
John Perfect	Martin Hoenigl
Peter Pappas	Oliver Cornely

Steering Committee

MSGERC	ECMM
Luis Ostrosky	Neil Gow
John Perfect	Martin Hoenigl
Peter Pappas	Oliver Cornely
George R Thompson	Johan Maertens
Dimitrios Kontoyiannis	Jean Pierre Gangneux
Monica Slavin	Connie Lass-Florl
Marisa Miceli	Patricia Munoz

Collaborative Working Groups

Aspergillus/Other Moulds	• Co-Chairs: Monica Slavin & Martin Hoenigl
Candida	• Co-Chairs: Joe Vazquez & Sevtap Arikan
Cocci/Other Endemics	• Co-Chairs: GR Thompson & Ana Alastruey Izquierdo
Cryptococcosis	• Co-Chairs: David Boulware & Tihana Bicanic

Consensus Agreements

Equal involvement (ECMM/MSGERC)	Experienced clinicians; include early career	Diversity (gender, geography, ethnicity)	Evidence-based
Transparency	Meetings closed to industry	Industry role: logistics funding and input	Listening sessions (WGs, Industry, FDA)
Bring in patient representatives for contribution on patient-important outcomes	Consult with microbiologists/ pharmacologists	Initial Face 2 Face Mtgs, later Zoom & Email follow-ups/edits	Publication/CME

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Other exploratory topics to be discussed

- DOOR
- PROs
- pediatrics
- Validation

Listening session- 1

- We will have four 5+1 minute slots for industry and agencies
- Open registration, but priority has been given to agencies and to companies that have contributed
- Speaking Slots (moderators will enforce time)
  - *Sanjay Revankar (FDA)*
  - *Gurjinder Bains (Shionogi)*
  - *John Rex (F2G)*
  - *Oscar Guzman (T2 Biosystems)*
- Moderators will enforce times
- Open Discussion- related to fungal disease response criteria
- Post-Session Comments/Questions - headquarters@msgerc.org

Next Steps: Working Group Meetings, Future Listening Sessions

- Paced online work
- In-person touch points:
  - *(Aspergillus/Other Moulds working group) – AAAM, Milan, Jan 23 & 24, 2024*
  - *(Aspergillus/Moulds & Candida working groups) – ECCMID, Barcelona, April 2024*
  - *Future WG Sessions- all working groups, in planning*
  - *Future Listening Sessions – Post ECCMID and beyond*

Projected Completion

MSGERC Biennial Meeting

September 4-6, 2024

Cheyenne Mountain Resort

Colorado Springs, CO, USA

More feedback?

Please send additional comments to:

- *Headquarters@msgerc.org*
- *president@ecmm.info*
- *Luis Ostrosky (luis.Ostrosky-zeichner@uth.tmc.edu)*
- *Martin Hoenigl (martin.hoenigl@medunigraz.at)*