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Infectious Diseases

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Rojek A, Dunning J, Olliaro P. Monkeypox: how will we know if the treatments work? *Lancet Infect Dis* 2022; published online Aug 2. https://doi.org/10.1016/S1473-3099(22)00514-X.

Table 1: Options for **primary** outcomes for clinical trials evaluating treatment safety and efficacy for Monkeypox.

Proposed outcome	Possible variations	Best suited to	Pros	Cons
Time to lesion resolution	• Time to resolution of *active* lesions • Time to *complete resolution* of all lesions • Proportion of (*active)* lesions resolved	Typical disease in patients without complications	• 'Time-to' analysis • Patient focused outcome. • Possibly the best clinical proxy of infectiousness	• Fails to capture patients without lesions • Fails to capture other manifestations (e.g. proctitis) • Healing time impacted by bacterial super-infection or surgical intervention • Inter-rater reliability of defining lesion not known. • No agreed definition of an *active* lesion or *completely resolved* lesion • Difficult to assess mucosal and genital lesions
Viral kinetics	• Variation in site – throat, blood, lesion that sample collected • Time to negative sample vs more detailed kinetics • PCR vs viral culture	Inpatients	• 'Time to' analysis • More direct correlation with antiviral effect.	• Difficulty obtaining samples in isolating patients • Pain or inconvenience of sampling for patients • Lack of longitudinal biologic sampling available in literature to inform design • Detection by PCR may not represent detection of live virus
Composite ordinal scale e.g. a) All active lesions resolved b) Active lesions c) Hospitalised with complicated monkeypox d) Death	Many possible	• Severe disease • Diverse disease presentation	• Patient focused outcome • Ordinal scale analysis	• Difficulty with ensuring mutual exclusivity of elements of the scale • No agreed definition on *severe* or *complicated* monkeypox • Fails when there is a narrow spectrum of disease severity
Lesion-based ordinal scale e.g. (a) All lesions completely resolved b) All active lesions resolved c) Active lesions but no new lesions d) New lesions occurring	Many possible	Non-hospitalised patients with low risk of death.	• Patient focused outcome • Ordinal scale analysis	• Fails to capture patients without lesions • Fails to capture other manifestations (e.g. proctitis) • Healing time impacted by bacterial super-infection or surgical intervention • Inter-rater reliability of defining lesion not known. • No agreed definition of an *active* lesion or *completely resolved* lesion • Difficult to assess mucosal and genital lesions