Outcomes of the deliberations of the WHO clinical expert group for monkeypox

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Comprehensive set of clinical and IPC interventions to care for patients with suspected or confirmed MPX from diagnosis to discharge

- Screening, triage and clinical evaluation for severity/complications using standardized protocols
- Prompt isolation and rapid implementation of appropriate IPC measures
- Testing to confirm diagnosis
- Symptomatic management of patients with mild or uncomplicated monkeypox (pain control, nutrition and antipyretics)
- Monitoring for and treatment of complications and life-threatening conditions such as progression of skin lesions, soft tissue infections, ocular problems, severe dehydration, severe pneumonia or sepsis, severe pain, urinary retention.
- Considerations for caring for pregnant women, children
- Use of therapeutic antiviral under randomized clinical trials to generate evidence on efficacy and safety. If not possible, then under protocols with harmonized data collection WHO's Global Clinical Platform for Monkeypox, would represent a desirable minimum dataset in the context of an outbreak, including the current event.
WHO Clinical Platform for Monkeypox to increase our understanding of clinical characterization

Objectives:
• Describe the clinical characteristics of monkeypox, including disease severity;
• Assess the variations in clinical characteristics of monkeypox;
• Identify the association of clinical characteristics of monkeypox with outcomes; and
• Describe the associations of interventions for MPX and outcomes (for interventions used outside of clinical trials)

Harmonized data collection tools
• One CRF with 3 modules: admission/initial visit, follow up, outcome/discharge
• Can be directly entered into the electronic WHO Platform (secure, password-protected platform) or sharing established databases or from printed paper CRFs, with data entered in the WHO Platform afterwards.
WHO Global Clinical Platform for Monkeypox

Steps to contribute to the platform:
• Create your profile by completing REGISTRATION FORM
• Review the Terms of Use
• After a few days, you will receive an email with the login credentials to access the WHO Platform, or, if you are sharing an established database, additional instructions to contribute data.

Outputs:
• Dashboard with visualizations of descriptive data
• Detailed global and regional reports

For any additional questions, please contact: monkeypox_clinicaldataplatform@who.int

https://tinyurl.com/GC19CDDP
Emerging clinical evidence


- Common symptoms: rash, malaise (96%), sore throat (78%), lymphadenopathy (57%)
- Common signs: rash, lymphadenopathy – the cervical region was most frequently affected [85.6%], followed by the inguinal region [77.3%]); and mouth/throat lesions (28.7%)
- Severity: higher maximal lesion counts, higher MPX viral DNA in blood, day of admission AST/ALT, neurologic impairment and respiratory impairment associated with poor outcomes
- Three deaths in children < 12 years of age.

UK (14-25 May 2022): 54 MPX-confirmed patients cared for at open-access sexual health clinics

- Common symptoms: fatigue or lethargy (67%), fever (57%)
- Common signs: all with rash most at the anogenital area (94%), > 1 anatomical site affected (89%), 55% with lymphadenopathy
- Severity: 9% admitted to hospital for localized cellulitis requiring antibiotics and for pain control
- No fatal outcomes reported.

https://doi.org/10.1101/2022.05.26.22273379
https://doi.org/10.1016/S1473-3099(22)00411-X
Considerations for CORE protocol endpoints

Limited clinical characterization data available to inform

• A robust Delphi process that is commonly used to develop outcomes not considered feasible.
• Thus, a decision to convene clinical experts with previous or current experience caring for patients with MPX on 2 occasions using the PALM 007 protocol endpoints as base for discussion.

Overarching themes from the discussion:

• Final choice of endpoints is dependent on the study design: inpatient vs outpatient.
• Minimal data collection important to not overburden research staff for the CORE protocol, especially in outpatient setting--what is feasible globally?
• Use of sub-studies to address other important research questions (transmission, IPC) with CORE trial framework, considered exploratory.
**Proposed CORE Protocol: Primary Endpoint**

<table>
<thead>
<tr>
<th><strong>Inpatients</strong></th>
<th><strong>Outpatients</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY ENDPOINT:</strong> Resolution of lesions (primary PALM 007)</td>
<td><strong>Proportion of patients with all lesions resolved at pre-specified time points (i.e., every 3-5 days, TBD)</strong></td>
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<tr>
<td>Time to resolution of all lesions (including skin and mucosa), up to 28 days after randomization (daily data collection)</td>
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</tbody>
</table>

**Time to lesion resolution**: lesions of skin and mucosa are crusted; scabs have fallen off and a layer of skin has formed underneath.

**Rationale:**
- Suggestion to keep this aligned with the PALM 007 primary outcome.
- Lesion resolution is both an important patient-centered outcome and an important public health outcome for onwards transmission.
- It is easily counted in some regions (legs or arms) but may be more complicated to count in some regions such as anal or oral mucosa regions.
- Thus, good training must be done on clinical evaluation of lesions to reduce inter-observer variability.
Proposed CORE Protocol: Secondary Endpoints

**SECONDARY ENDPOINT:**
All-cause mortality at 28 days
 (*secondary PALM 007*)

**Rationale:**
- All-cause mortality more reliably measured than MPX-specific mortality.
- Removed PALM 007 time to 28 mortality to reduce data collection burden.
- Important patient centered outcome, reliable and easy to measure.
- But expect very few event rates.

Applies to inpatients and outpatients.
Proposed CORE Protocol: Secondary Endpoints

Rationale:

- Added as most patients will be managed at home or in community.
- All-cause hospitalization rather than MPX specific to ease data burden.
- Important patient centered and health system outcome.
- Easy to measure.
- Understanding however that admission practices will vary according to jurisdiction.
Proposed CORE Protocol: Secondary Endpoints

SECONDARY ENDPOINTS:

Complications: proportion of patients with a complication

(expanded from PALM 007)

Complications include:
- genitourinary (urinary retention),
- lower respiratory tract (pneumonia, need for oxygen),
- ocular impairment,
- neurologic impairment,
- antibiotics for secondary bacterial skin infection,
- severe pain

Rationale:
- Progression to complications is an important patient-centered outcome and important health system outcome to prepare clinical services for MPX cases.
- Limit to most relevant complications.
- Easy to measure, as long as definitions are clear and staff is trained.
Proposed CORE Protocol: Secondary Endpoints

**SECONDARY ENDPOINTS:**

**Symptoms and signs**  
*(secondary in PALM 007)*

**Inpatients:** frequency and duration of clinical symptoms (daily data collection)

**Outpatients:** frequency of signs and symptoms at baseline and at end of study

**Rationale:**

- Collection of symptoms and signs can be useful to understand the clinical characterization, however, will require intensive data collection.
- Suggestion to limit signs/symptoms to most important.

**Symptoms** include nausea, vomiting, abdominal pain, anorexia, cough, dysphagia, odynophagia, fever, headache, oral pain, pain with urination, rectal pains

**Signs** include including lymphadenopathy, ocular lesions, urethritis, and proctitis
Proposed CORE Protocol: Secondary Endpoints

Rationale:

- Important to collect standardized data for adverse events to increase our understanding of safety.

Adverse event (AE):

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
## Proposed CORE Protocol: Exploratory Endpoints

<table>
<thead>
<tr>
<th>EXPLORATORY ENDPOINTS:</th>
<th>PRIMARY ENDPOINT:</th>
<th>Rationale:</th>
</tr>
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<tbody>
<tr>
<td><strong>Sub-studies:</strong></td>
<td><strong>Resolution of lesions</strong></td>
<td>• Daily sampling is labor intensive and likely only to be done for hospitalized patients.</td>
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<tr>
<td>viral trajectories</td>
<td></td>
<td>• Taking sample at randomization and at day 5 to be coordinated with lesion evaluation is pragmatic and could be done as outpatients.</td>
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<tr>
<td>(exploratory in PALM 007)</td>
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<td>• Removed the outcome of two negative blood PCRs as did not seem relevant to MPX.</td>
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</tbody>
</table>

### Inpatients
- Time to the first negative blood, oropharyngeal (OP) and rectal swab PCR result up to 28 days after randomization (without the requirement of a second consecutive negative).

### Outpatients
- Proportion of viral load negative from blood, OP and rectal swabs assessed at day set time points (every 3-5 days, to be determined).

### Optional:
- Correlation of CT values and infectious virus
- Environmental sampling for viral PCR and infectious virus
- Sampling from semen, vaginal fluid and breast milk
Proposed CORE Protocol: Exploratory Endpoints

**Rationale:**

- Use standardized approach to classify affected body regions/areas: body areas involved, including arms/hands; legs/feet; genital area (including perineum), oral mucosa, peri-anal area,
Next steps

Strengthen evidence base to inform development of best practice guidelines for clinical management and IPC for MPX.

• Finalise CORE Protocol and implementation for therapeutics
• Contributions to the WHO Clinical Data Platform for monkeypox
• Develop GRADE–based Guidelines for Clinical Management and IPC for MPX
Thank You!