PLATINUM

Placebo-controlled randomised trial of tecovirimat in non-hospitalised monkeypox patients

Statistical Analysis Plan

Version 1.0

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Abbreviations

CCO	Central Coordinating Office
DMC	Data Monitoring Committee
eCRF	Electronic case report form
ITT	Intention to treat

1 INTRODUCTION

This document details the proposed presentation and analysis for the main paper reporting results from the PLATINUM randomised controlled trial. Any subsequent analyses of a more exploratory nature will not be bound by this strategy. Suggestions for subsequent analyses by oversight committees, journal editors or referees, will be considered carefully in line with the principles of this analysis plan.

Any deviations from the statistical analysis plan will be described and justified in the final report. The analysis will be carried out by identified, appropriately qualified and experienced statisticians, who will ensure the integrity of the data during their processing.

This SAP is based on the protocol, which can be found on the trial website https://www.platinumtrial.ox.ac.uk/more-information.

2 BACKGROUND INFORMATION

2.1 Rationale

In 2022 an outbreak of monkeypox was identified in the UK, which soon afterwards was recognized to be part of an unprecedented global epidemic involving sustained person-to-person transmission.[1] There are no antiviral treatments of proven benefit for monkeypox, and there have previously been no randomised trials evaluating antiviral treatments. Tecovirimat is an antiviral developed for the treatment of smallpox that also has efficacy in animal models of monkeypox infection. When given to healthy volunteers, tecovirimat has appeared safe and well tolerated, but there is no randomised data on efficacy in humans with monkeypox infection.[2] The PLATINUM trial aims to provide reliable evidence on the efficacy and safety of oral tecovirimat for the treatment of acute monkeypox among patients who do not require admission to hospital.

2.2 Objectives of the trial

The primary objective is to provide a reliable estimate of the effect of tecovirimat on the time to resolution of monkeypox skin and mucosal lesions. Secondary objectives are to estimate the effect of tecovirimat on the time to clearance of infectious monkeypox virus, and on the time to improvement in pain related to monkeypox.

2.3 Trial design

PLATINUM is a randomised controlled trial, in which participants will be allocated in a 1:1 ratio to tecovirimat or placebo. The trial will be open to patients across the UK and aims to

recruit 500 participants with confirmed monkeypox, who will be followed-up for 28 days. It will use a remote design, including online forms for self-assessment of lesion resolution and follow-up calls from staff at the Central Coordinating Office (CCO). Couriers will deliver tecovirimat or matching placebo to participants, and collect weekly self-taken swabs for analysis at a central laboratory.

2.4 Eligibility

2.4.1 *Inclusion criteria*

Patients are *eligible* for the study if **all** of the following are true:

(i) Laboratory-confirmed monkeypox infection
(ii) The presence of active skin or mucosal lesion(s)[a]
(iii) Patient is appropriate to be managed without hospitalisation
(iv) For women with reproductive potential,[b] willingness to use effective contraception[c] from the time of enrolment through study day 28

2.4.2 *Exclusion criteria*

Patients are to be *excluded* if **any** of the following are true:

(i) Weight <13 kg (children weighing more than this are eligible)
(ii) Planned use of contraindicated treatment (see protocol section 2.2.5) during study period
(iii) Current or past use of tecovirimat
(iv) Lack of capacity to provide informed consent
(v) The referring doctor considers there to be a definite indication for tecovirimat
(vi) Hypersensitivity to tecovirimat or any excipients in the study treatment
(vii) Current pregnancy or breastfeeding
(viii) Clinically determined severe renal impairment, i.e. under the care of a nephrologist
(ix) Clinically determined severe hepatic impairment, i.e. under the care of a hepatologist
(x) Diagnosis of epilepsy

2.5 Treatment

Randomised participants will be issued with a supply of tecovirimat capsules (200mg) or matching placebo capsules to be taken orally with food for 14 days as follows:

- Adults aged ≥18 years: three capsules twice a day (total daily tecovirimat dose 1200 mg)
- Children and adolescents aged <18 years:
  - Estimated body weight ≥13 to <25 kg: one capsule twice a day (total daily tecovirimat dose 400 mg)

[a] An active lesion is a skin lesion that is not scabbed or desquamated or a mucosal lesion that has not healed.
[b] Female reproductive potential is defined as the time following menarche until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
[c] Acceptable methods of effective contraception include the following: intrauterine devices; progestogen-only injections, pill or implant; combined hormonal contraception (pill, patch or vaginal ring); male or female condom; diaphragm or cervical cap with a spermicide.

- Estimated body weight ≥25 to <40 kg: two capsules twice a day (total daily tecovirimat dose 800 mg)
- Estimated body weight ≥40 kg: three capsules twice a day (total daily tecovirimat dose 1200 mg)

2.6 Outcomes

2.6.1 *Primary outcome*

Time (in days) to active lesion resolution, defined as the first day on which all skin lesions are scabbed or desquamated (and mucosal lesions healed), up to 28 days after randomisation.

2.6.2 *Secondary clinical outcomes*

(i) Time (in days) to complete lesion resolution, defined as the first day on which all lesions are completely resolved (all scabs dropped off and intact skin remains underneath, and mucosal lesions healed), up to 28 days after randomisation

(ii) Time to negative throat swab viral culture, defined as time to consistently negative culture for monkeypox virus on throat swab at Days 7, 14, 21, and 28

(iii) Time to negative skin or mucosa swab viral culture, defined as time to consistently negative culture for monkeypox virus on swab of most recent active skin or mucosa lesion at Days 7, 14, 21, and 28

2.6.3 *Subsidiary clinical outcomes*

(i) Clinical status on day 7, 14, 21 and 28 according to the following ordinal scale:
   a. All lesions completely resolved (all scabs dropped off and intact skin remains underneath, and all mucosal lesions healed)
   b. Active lesions resolved (all skin lesions scabbed or desquamated, but not all completely resolved)
   c. Active lesions persist but no new lesions in last 24 hours
   d. New active lesion(s) in last 24 hours.

(ii) Throat swab monkeypox DNA levels: monkeypox virus DNA concentration in throat swabs at Days 7, 14, 21, 28

(iii) Number (%) of patients admitted to hospital for a complication of monkeypox (overall and by type)

(iv) Time to sustained absence of use of analgesia for monkeypox symptoms, defined as time to consistently reporting no use of analgesia, up to 28 days after randomisation.

2.6.4 *Safety assessments*

(i) Number (%) of patients suffering serious adverse events (overall and by type) within 28 days of randomisation

(ii) Number (%) of patients suffering adverse events of special interest (overall and by type) within 28 days of randomisation. These are:
   - Vomiting
   - Diarrhoea
   - Fever
   - Severe tiredness
   - Swollen lymph glands
   - Headache

- Muscle or joint pain
- Sore eyes
- Shortness of breath
- Secondary skin infection
- Pain related to monkeypox symptoms

(iii) Number (%) of patients suffering death, overall and by cause

(iv) Reasons for prematurely stopping allocated study treatment

2.6.5 *Exploratory analyses*

Other analyses may be conducted to explore the effects of tecovirimat vs. placebo on clinical efficacy, safety and microbiological outcomes, including in subsets of patients defined by baseline characteristics and medical history (with appropriate caution in the interpretation of the exploratory nature of these analyses and the multiple number of such comparisons).

2.7 Hypothesis framework

For each of the primary, secondary and subsidiary outcomes, the null hypothesis will be that there is no true difference in effect between the tecovirimat and placebo arms.

2.8 Sample size

For the log-rank test of the primary endpoint 'time to active lesion resolution', the two key determinants of power are the total number of active lesion resolution events and the treatment-to-control ratio of the rate of active lesion resolution.

Table 1 displays the power of this test for various scenarios. In total, 318 patients with lesion resolution by day 28 are needed to detect a 40% improvement in the rate of lesion resolution as measured by the rate ratio (akin to a "hazard ratio" but for a positive outcome instead of death; values greater than one indicate improved outcomes) with at least 85% power and a two-sided α of 0.05. Conservatively assuming that the observed event rate of 77% from the 2007-2011 INRB/USAMRIID observational study will apply to the combined time to event data of experimental and control groups yields a total targeted sample size of 413 participants.[3] A total sample size of 500 is planned to account for one interim analysis and approximately 10% losses to follow-up.

Table 1. Number of events needed to have 80% and 85% power at 2P=0.05 to detect an improvement in the primary outcomes.

Rate Ratio	Scenario for 80% Power (β=0.20)		Scenario for 85% Power (β=0.15)	
	Number of Events Needed	Number of Patients Needed*	Number of Events Needed	Number of Patients Needed*
1.30	457	594	522	678
1.40	278	362	318	413
1.50	191	249	219	285

* Assumes that 77% of patients will experience the event and does not account for potential dropout. In the 2007-2011 INRB/USAMRIID observational study, 77% of patients reached lesion resolution (as defined above) within 22 days.

Since the event rate is uncertain, the sample size will be reviewed and revised based on blinded data (i.e. with time to event data for the experimental and control groups combined), when about 50% of the originally planned number of participants have reached determination of the primary endpoint.

2.9 Randomisation

Eligible individuals who have provided and consent will be allocated to tecovirimat or placebo using a minimised randomisation program that helps maximise balance between the allocated treatment groups with respect to the following prognostic variables:

- Age (<18, ≥18-<40, ≥40)
- Sex at birth (male/female)
- Previous orthopoxvirus vaccination (yes/no/not known)
- Severity of rash (localised vs disseminated, defined as >1 body area affected)
- Days since onset of rash (≤7 days or >7 days)

The implementation of the randomisation procedure will be monitored by the Senior Trials Programmer, and the Trial Steering Committee notified if an error in the randomisation process is identified.

2.10 Blinding

PLATINUM is a placebo-controlled trial in order to avoid knowledge about the treatment allocation impacting (or being perceived to impact) the assessment of clinical outcomes and adverse events or adherence to the study procedures (e.g. completion of questionnaires or collection of samples). While the study is in progress, access to the treatment allocation for individual participants and tabular results of study outcomes by allocated treatment allocation will not be available to anyone other than the Data Monitoring Committee (DMC) and the statistical team responsible for preparing analyses for the DMC.

2.11 Data collection schedule

Baseline information will be entered into a web-based electronic case-report form (eCRF) by the CCO staff at the time of randomisation (day 0). Follow-up information will be collected using a daily eCRF completed by the participant on days 1-28, and a weekly eCRF completed by CCO staff during remote review on days 7, 14, 21 and 28. Participants will also be asked to self-collect swabs from their throat and most recent active skin or mucosal lesion at days 7, 14, 21, and 28 (each ±2 days). The same information will be collected from all study participants if possible, irrespective of whether they start or complete the scheduled course of allocated study treatment.

All randomised participants are to be followed up for 28 days after randomisation. Longer term (up to 1 year) follow-up may be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, the UK Health Security Agency and equivalent bodies. Additional follow-up calls may be conducted following the end of the main assessment period of the study (28 days) to assess complete resolution of monkeypox symptoms and other relevant adverse events.

2.12 Data monitoring

During the study, interim analyses of unblinded study data (including information on the pre-specified primary, secondary and safety outcomes) will be supplied in strict confidence to the independent DMC. The DMC will request such analyses at a frequency relevant to the stage of the study and the speed and volume of new information (typically every 6 months with a Chair's review at 3 months) or in response to emerging information from other studies.

The DMC will independently evaluate these analyses and any other information considered relevant. The DMC will review the analyses among children (age <18 years) both separately and combined with the adult data. The DMC is expected to advise the Chief Investigator and Chair of the Trial Steering Committee if, in the view of the DMC, there is compelling evidence of *hazard* that seems likely to outweigh any potential benefit (either overall or in a particular subgroup of participants).

A single interim assessment for *benefit* is to take place when 50% of the originally planned number of participants have reached determination of the primary endpoint (i.e. experienced active lesion resolution before or at day 28 or reached 28 days of follow-up). A group sequential design was used to generate asymmetric two-sided boundaries based on Hwang-Shih-DeCani alpha and beta spending functions for efficacy and non-binding futility assessments (**Table 2**).[4]

Table 2. DMC guidance for interim analysis of benefit

		Lower bounds (futility assessment)		**Upper bounds (efficacy assessment)**	
Analysis	**N**	**Z-statistic**	**P-value***	**Z-statistic**	**P-value***
Interim	216	0.42	0.6616	2.75	0.0030
Final	432	1.98	0.9762	1.98	0.0238

*One-sided p-values; the one-sided p-value of the final analysis of 0.0238 corresponds to a two-sided p-value of 0.0476. Boundaries estimated using R package gsDesign

The DMC will assess the effect of tecovirimat vs. placebo on the primary outcome against these criteria and advise the Chief Investigator accordingly. In considering its recommendations, the DMC should also take account of the totality of the evidence from the trial data (including effects on secondary and other outcomes and in key participant subgroups) and any other information from external sources that it considers relevant (e.g. results from other trials, emerging information on the nature of the disease and its epidemiology).

The Chief Investigator is responsible for considering the advice of the DMC in discussion with members of the Trial Steering Committee, amending the protocol accordingly, and making the information available to the public. Unless this happens, the Trial Steering Committee, Chief Investigator, study staff, investigators, study participants, funders and other partners will remain blind to the treatment allocation for individual participants and to the interim results until 28 days after the last patient has been randomised (at which point unblinded analyses may be conducted).

Further details about the role and membership of the independent Data Monitoring Committee are provided in the protocol.

2.13 Trial reporting

The trial will be reported according to the principles of the CONSORT statement.[5]

2.14 Analysis population

The intention to treat (ITT) population will be all participants randomised, irrespective of treatment received. This ITT population will be used for analysis of efficacy and safety data. For interim analyses, baseline data will be reported for all participants with data available and outcome data will be reported for all participants who have reached day 28 after randomisation.

3 DESCRIPTIVE ANALYSES

3.1 Participant throughput

The flow of participants through the trial will be summarised using a CONSORT diagram. This will describe the numbers of participants randomised, receiving allocated treatment, withdrawing consent, and included in the ITT analysis population.

3.2 Baseline comparability of randomised groups

The following baseline characteristics will be described separately for patients randomised to tecovirimat and placebo.

- Age at randomisation
- Sex at birth
- Time since onset of skin or mucosal lesions
- Number of active lesions (1-5, 6-25, 26-100, >100)
- Number with disseminated infection (defined as >1 body region affected)
- Proportion requiring painkillers for monkeypox
- Comorbidities (diabetes, HIV, and immunosuppression related to medication or haematological disease)
- Previous orthopoxvirus vaccination

3.3 Completeness of follow-up

The number and percentage of participants with follow-up information at day 28 after randomisation will be reported.

3.4 Adherence to treatment

The number and proportion of patients who did not receive the treatment they were allocated will be reported, as well as details of the number of days of treatment received.

4 COMPARATIVE ANALYSES

For all outcomes, pairwise comparisons will be made between the tecovirimat and placebo arms performed on the ITT population at 28 days after randomisation.

4.1 Outcomes

4.1.1 *Primary outcome*

The primary outcome is defined as the first day on which all skin lesions are scabbed or desquamated and mucosal lesions healed, up to 28 days after randomisation (regardless of whether active, unscabbed, lesions are reported on subsequent days). Missing values for a particular day will be imputed as the reported value taken nearest in time before or afterwards (counted in whole days; in the event of a tie the reported value taken beforehand will be used).

For time-to-event analyses of this outcome, the tecovirimat group will be compared with the placebo group using a stratified log-rank test (days since symptom onset $\leq$7 and >7 days). Kaplan-Meier estimates for the time to event will also be plotted, with associated log-rank p-values. The log-rank 'observed minus expected' statistic (and its variance) will also be used to estimate the average event rate ratio (and its confidence interval) for those allocated to tecovirimat vs placebo.

4.1.2 *Secondary outcomes*

Secondary outcome (i) is defined as the first day on which all skin lesions are completely resolved, meaning all scabs have dropped off with intact skin remaining underneath, and mucosal lesions have healed, up to 28 days after randomisation (regardless of whether unhealed lesions are reported on subsequent days). Imputation of missing data and the method of time-to-event analysis will be as for the primary outcome above.

The remaining secondary outcomes are defined as the time to consistently negative culture for monkeypox virus in serial self-collected swabs, either taken from the throat (secondary outcome (ii)), or the most recent active skin or mucosal lesion (secondary outcome (iii)). These swabs are collected on days 7, 14, 21, and 28 after randomisation, and will be analysed using an interval censored Weibull model. A negative culture will be considered 'consistently negative' if it is not followed by a positive culture on the same type of swab during subsequent assessments.

4.1.3 *Subsidiary outcomes*

Clinical status on an ordinal scale will be compared between tecovirimat and placebo groups using a proportional odds model.[6] Howard's method will be used if the proportional odds assumption is not satisfied.[7] Monkeypox virus DNA concentration will be compared between groups using the Wilcoxon rank-sum test.

Time to sustained absence of use of analgesia for monkeypox symptoms is defined as the first day from which analgesia is consistently not required until day 28. Imputation of missing data and the method of time-to-event analysis will be as for the primary outcome above.

4.1.4 *Safety outcomes*

The number and percentage of patients suffering suspected serious adverse reactions, suspected unexpected serious adverse reactions, and death (overall and by cause), will be listed by trial allocation. Adverse events of special interest (listed in 2.6.4) and reasons for study drug discontinuation, will be presented by randomised group as counts and percentages. Where possible, the absolute risk differences will be presented with confidence intervals, analysed using Fisher's exact test.

4.2 Pre-specified subgroup analyses

Pre-specified subgroup analysis will be conducted for the primary outcome using the statistical test for interaction (or test for trend where appropriate). Results will be presented on forest plots as event rate ratios with confidence intervals. The following subgroups will be examined based on information at randomisation:

- Age (<18, 18-39, ≥40)
- Sex (male/female)
- Orthopoxvirus vaccination status (ever received yes/no)
- Time since onset of first lesion (≤7 days or >7 days)

4.3 Adjustment for multiple testing

A step-down approach will be used to control the family-wise error rate across the primary and three secondary outcomes: Hypothesis testing will first be conducted for the primary (time to active lesion resolution). Only if the null hypothesis is rejected at a 2-tailed p=0.0476, confirmatory analysis of the three secondary endpoints will be performed at a 2-tailed p=0.0476. To account for multiplicity of testing of the three secondary endpoints, the Benjamini-Hochberg method will be used.[8] For all other assessments (including those of subsidiary, safety, and exploratory assessments and any subgroup assessments) due allowance will be made in their interpretation for multiple comparisons.

4.4 Statistical software employed

The statistical software SAS version 9.4 and R Studio 3.6.2 (or later) for Windows will be used for the interim and final analyses.

4.5 Additional post-hoc exploratory analysis

Any post-hoc analysis requested by the oversight committees, a journal editor or referees will be labelled explicitly as such. Any further future analyses not specified in the analysis protocol will be exploratory in nature and will be documented in a separate statistical analysis plan.

5 REFERENCES

5.1 Trial documents

The study protocol, case report forms and statistical analysis plan are published on the trial website (www.platinumtrial.ox.ac.uk/more-information).

5.2 Other references

1. Thornhill, J. P. *et al.* Monkeypox Virus Infection in Humans across 16 Countries - April-June 2022. *N Engl J Med* **387**, 679–691 (2022).
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6 DOCUMENT HISTORY

Version	Date	Edited by	Comments/Justification	Timing in relation to unblinded interim monitoring	Timing in relation to unblinding of Trial Statisticians
1.0	21/11/22	LP	First draft	Prior	Prior