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Low-dose trimethoprim-sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (LOW-TMP): protocol for a phase III randomised, placebo-controlled, dose-comparison trial

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ABSTRACT

Introduction *Pneumocystis jirovecii* pneumonia (PJP) is an opportunistic infection of immunocompromised hosts with significant morbidity and mortality. The current standard of care, trimethoprim-sulfamethoxazole (TMP-SMX) at a dose of 15–20 mg/kg/day, is associated with serious adverse drug events (ADE) in 20%–60% of patients. ADEs include hypersensitivity reactions, drug-induced liver injury, cytopenias and renal failure, all of which can be treatment limiting. In a recent meta-analysis of observational studies, reduced dose TMP-SMX for the treatment of PJP was associated with fewer ADEs, without increased mortality.

Methods and analysis A phase III randomised, placebo-controlled, trial to directly compare the efficacy and safety of low-dose TMP-SMX (10 mg/kg/day of TMP) with the standard of care (15 mg/kg/day of TMP) among patients with PJP, for a composite primary outcome of change of treatment, new mechanical ventilation, or death. The trial will be undertaken at 16 Canadian hospitals. Data will be analysed as intention to treat. Primary and secondary outcomes will be compared using logistic regression adjusting for stratification and presented with 95% CI.

Ethics and dissemination This study has been conditionally approved by the McGill University Health Centre; Ethics approval will be obtained from all participating centres. Results will be submitted for publication in a peer-reviewed journal.

Trial registration number NCT04851015.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be one of the largest randomised trials of *Pneumocystis jirovecii* pneumonia treatment carried out in the last 30 years.
⇒ The population of the study will include better representation of women, older adults, and non-HIV immune suppressed populations.
⇒ Clinically relevant endpoint of change of treatment, new mechanical ventilation, or death by day 21 will be studied.
⇒ Generalisability of the study is limited by inclusion of patients only from tertiary care North American centres.

INTRODUCTION

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic fungal infection primarily affecting immunocompromised patients.[1] Infection with *P. jirovecii* is common and usually occurs in early childhood; most individuals show serological evidence of a clinically insignificant infection by age 4.[1 2] However, immunocompromised patients—those with HIV (particularly CD4 ≤200 cells/µL), solid organ and allogeneic haematopoietic stem cell transplant recipients, as well as patients on certain chemotherapies, immunosuppressant drugs and systemic corticosteroids—are at a higher risk of PJP.[3 4] Although routine primary prophylaxis has diminished its prevalence, PJP remains the most common opportunistic infection in North America. In 2017, it was responsible for 10 000 hospitalisations in the USA[5 6] and is responsible for approximately 400 000 cases per year worldwide.[7] PJP results in significant mortality with rates between 20%

and 50% among non-HIV populations[8–11] and 10%–20% for patients with HIV.[12–14]

Current guidelines from Centers for Disease Control and Prevention, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America and the American Society of Transplantation[15–18] recommend weight-based trimethoprim-sulfamethoxazole (TMP-SMX) at a dose of 15–20 mg/kg/day of the TMP component as the standard of care. Higher doses of TMP-SMX are associated with hypersensitivity reactions, drug-induced liver injury, cytopenias and renal failure.[19–27] A daily dose of >15 mg/kg is an independent predictor of adverse drug events (ADEs)[28] with the frequency of haematological and renal adverse events increasing in a dose-dependent manner.[29] ADEs have been reported among 20%–60%[30–36] of patients and up to 40% have discontinued therapy due to drug intolerance in previous randomised controlled trials (RCTs).[30 31 33] Recommendation for the current standard-of-care dose comes from a small underpowered study of children with leukaemia[37] and studies that primarily included young men with HIV[30 33 38–45]; these studies did not capture the modern-day population treated for PJP, which is composed of adults with polypharmacy, patients with renal insufficiency, solid-organ transplant patients prescribed calcineurin inhibitors and patients with pre-existing bone marrow suppression.[46–48] The modern epidemiology of PJP translates to toxicity risks that are much higher than in the past. Therefore, despite being the standard of care for PJP, maximal effectiveness of TMP-SMX is partly curtailed by its poor ADE profile at higher doses.

To better inform the optimal dosing strategy for PJP therapy, we recently performed a systematic review and meta-analysis of reduced dose regimens of TMP-SMX in the treatment of PJP among immunocompromised adult patients with and without HIV.[49] When comparing standard doses to reduced doses (≤10 mg/kg/day of the TMP component), there was no statistically significant difference in mortality (absolute risk difference: −9% in favour of reduced dose, 95% CI −27% to 8%) with a corresponding 18% (95% CI −31% to −5%) absolute risk reduction of grade 3 or higher ADEs. These data provide the best available evidence for treatment equipoise and highlight the need for a RCT to directly compare dosing strategies. Given the significant mortality of PJP and the high rates of treatment-limiting ADEs, this definitive study demonstrating that reduced dose TMP-SMX (10 mg/kg/day) is superior to the current standard-of-care dose of 15–20 mg/kg/day would have major practice-changing implications worldwide.

METHODS

Objective

The primary objective of this trial is to determine whether treatment with reduced-dose TMP-SMX (10 mg/kg/day) is superior to a selected standard dose (15 mg/kg/day) among immunocompromised HIV-infected and uninfected patients with PJP for the composite primary outcome of change of treatment, new mechanical ventilation or death by day 21.

Design

The study is a double-blind, placebo-controlled RCT. The trial is considered a phase III study by Health Canada as we are studying a new dose for TMP-SMX and has received a No Objection Letter. The study outline is presented in figure 1. The study will be conducted in accordance with Good Clinical Practice, Health Canada requirements, the Declaration of Helsinki and ethical principles.

Sites

The trial will be led by and coordinated from the Research Institute of the McGill University Health Centre (MUHC) as the sponsor of the Health Canada protocol. Participant enrolment and follow-up will commence at MUHC sites (Montreal General Hospital and Royal Victoria Hospital) in Summer 2022 and conclude in Fall 2024 at all sites. Recruitment for the trial will subsequently be undertaken at 16 Canadian hospitals in five provinces (table 1). There will be at least monthly meetings with all Canadian site investigators. There will be regular audits to ensure protocol compliance, verify the validity of case records and ensure meticulous record keeping.

Participant screening and eligibility

Patients presenting to day hospitals, emergency departments or inpatient units who are diagnosed with PJP, will be identified by treating physicians from relevant clinical services—notably, respirology, haematology-oncology, critical care, internal medicine, infectious disease and

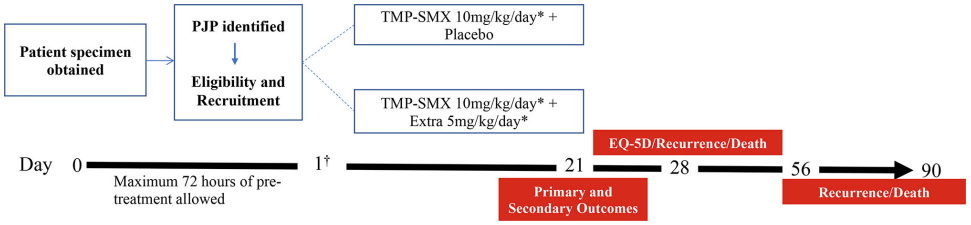

Figure 1 Study design diagram. *50% dose reduction if CrCl 16–30 mL/min; 75% dose reduction if ≤15 mL/min. †Day 1 will represent first dose of study drug. PJP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole. (uploaded separately).

Table 1 Participating sites and estimates cases per site

Centre	No of sites	City	Province	PJP cases
University of Alberta Hospital	1	Edmonton	AB	10
University of Calgary	2	Calgary	AB	50
University of British Columbia	2	Vancouver	BC	15
University of Manitoba	1	Winnipeg	MB	10
St. Michael's Hospital	1	Toronto	ON	15
University Health Network	2	Toronto	ON	20
University of Ottawa	2	Ottawa	ON	25
Jewish General Hospital	1	Montréal	QC	10
McGill University Health Centre	2	Montréal	QC	35
University of Sherbrooke	2	Sherbrooke	QC	10
Total	16			200

PJP, *Pneumocystis jirovecii* pneumonia.

transplant. Individuals who are within 72 hours of initial therapy for PJP, over the age of 18 years, and meet the prespecified inclusion and exclusion criteria (box 1), will be invited to participate with informed consent by a research coordinator from the study team.

The diagnosis of PJP will be made based on predetermined criteria. A definitive diagnosis of PJP will be made with identification of the organism microscopically in tissue, bronchoalveolar lavage fluid or expectorated sputum using conventional or immunofluorescence staining. In situations where a definitive diagnosis cannot be made, a probable diagnosis will be based on the Consensus Definitions of Invasive Fungal Disease From the European Organisation for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium.[50] Specifically, a probable diagnosis of PJP will be made in the presence of at least one host factor, one clinical feature, in conjunction with mycological evidence (two elevated serum levels of beta-D-glucan ≥80 ng/L or detection by PCR). In this case, the patient will be referred to as 'presumptive PJP' and this will comprise a prespecified subgroup for analysis. Complete definitions of definitive and presumptive diagnoses are presented in box 2.

With the advent of chemoprophylaxis and widespread use of highly active antiretroviral therapy, the incidence, hospitalisation and mortality of PJP in HIV-infected patients has greatly reduced.[5] By contrast, PJP in HIV-uninfected patients has increased as the number of patients receiving antitumour chemotherapeutic agents, immunosuppressive therapy and organ transplantation is growing. Moreover, this latter suffers from more comorbidity, more drug–drug interactions and a propensity towards fulminant disease with higher rates of mortality.[13 14] While our study will primarily consist of non-HIV patients; we will stratify randomisation to include HIV patients as well.

Box 1 Study inclusion and exclusion criteria

Inclusion

1. Age 18 or older.
2. Immunocompromised with or without HIV infection CD4 count <500 cells/mm^3 (including but not limited to solid-organ transplant, solid tumours, haematological stem cell transplant and malignancies, systemic diseases, chemotherapy, long-term corticosteroid use and immunosuppressive therapies, as well as primary immunodeficiencies).
3. Presenting to a day hospital, emergency department or admitted to hospital.
4. Proven or presumptive diagnosis of *Pneumocystis jirovecii* pneumonia (PJP) (box 2).

Exclusion

Clinical:

1. Previous severe adverse reaction to trimethoprim-sulfamethoxazole (TMP-SMX) or hypersensitivity to any sulfa drug or any component of the formulation.
2. PJP prophylaxis for ≥4 weeks with TMP-SMX at enrolment.
3. More than 72 hours of any therapy for PJP.
4. Hepatic impairment marked by alanine aminotransferase levels ≥5 times the upper limit of normal.
5. Known G6PD deficiency.
6. Known diagnosis of porphyria.
7. Known pregnancy or breast feeding (as per Health Canada).

Administrative: Unable to provide informed consent and no available healthcare proxy (with ethics approval for deferred consent in cases of critical illness); refused consent; no reliable means of outpatient contact (telephone/email/text).

Randomisation and study intervention

Participants meeting the eligibility criteria and providing informed consent will be enrolled into the study. All patients will receive an open label dose of 10 mg/kg/day of the TMP component (rounded to nearest half tablet or the nearest 40 mg of trimethoprim component if intravenous formulation is prescribed) and will then be randomised 1:1 to receive an additional 5 mg/kg/day of

Box 2 Definitive and presumptive diagnosis of *Pneumocystis jirovecii* pneumonia (PJP) based on consensus definitions of invasive fungal disease from the European Organisation for research and treatment of cancer and the mycoses Study Group education and research Consortium

Presumptive diagnosis of PJP:
Appropriate host factors and clinical and radiologic criteria, plus:
⇒ Amplification of *P. jirovecii* DNA by quantitative real-time PCR in respiratory specimen.
⇒ Detection of ß-D-glucan ≥80 ng/L (pg/mL) in ≥2 consecutive serum samples provided other aetiologies have been excluded.

Definitive diagnosis of PJP
Clinical and radiologic criteria, plus:
⇒ Demonstration of *P. jirovecii* by microscopy using conventional or immunofluorescence staining in tissue or respiratory specimens.

Host factors
⇒ Low CD4 lymphocyte counts <200 cells/mm^3 (200×106 cells/L) induced by a medical condition, including HIV, anticancer, anti-inflammatory and immunosuppressive treatment, including by not limited to:
  ⇒ Primary immunodeficiencies with numeric/functional T-cell deficiency.
  ⇒ Acute leukaemia, non-Hodgkin's lymphoma, solid tumours, allogenic haematological stem cell transplant.
  ⇒ Solid-organ transplantation.
  ⇒ Autoimmune and hyperinflammatory disorders, including treatment with agents that lead to functional T-cell deficiencies.
⇒ Use of therapeutic doses of ≥0.3 mg/kg prednisone equivalent for ≥2 weeks in the past 60 days

Clinical features
⇒ Fever.
⇒ Respiratory symptoms with cough, dyspnoea and hypoxaemia.
⇒ Extensive, mostly diffuse Ground Glass Opacities (GGO) on CT scans, which typically has an upper lobe and perihilar predominance, sometimes with peripheral sparing or a mosaic pattern; consolidations, small nodules and unilateral infiltrates are less frequent.
⇒ Bilateral or diffuse GGO on X-ray with interstitial infiltrates as the predominant feature; alveolar, alveolar-interstitial and unilateral infiltrates are less frequent.

TMP (control) or placebo (experimental). Adjusted body weight will be used if the patient is ≥120% of ideal body weight.[51] Creatinine clearance will be calculated using the Cockcroft-Gault Equation.[52] The dose will be reduced by 50% at creatinine clearances of 16–30 mL/min and by 75% at creatinine clearances of ≤15 mL/min. Our dosing calculator is available for download at http://tmpdose.idtrials.com. The actual dose used will be approximately 9.5–10.5 mg or 14.5–15.5 mg based on the closest multiple of half tablets. As the oral bioavailability of TMP-SMX is equivalent to the intravenous, the drug can be administered in either form at the discretion of the treating team.[53] Health Canada has approved this dosing strategy. Sites will use locally available generic forms of TMP-SMX.

Randomisation will occur centrally at the MUHC through Research Electronic Data Capture and will be performed by permuted blocks with randomly mixed block sizes of 4, 6 and 8. To ensure the two groups are balanced in areas where we expect differences in outcomes or severity of TMP-SMX side effects, we will stratify by: HIV serostatus; renal function (≤30 mL/min, >30 mL/min) and disease severity at enrolment (supplemental oxygen <40% vs ≥40%; evaluated based on guidelines for oxygen use in hospitalised patients.[54] Allocation concealment will ensure the research coordinator or physician enrolling the participant has no prior knowledge of treatment arm assignment. Furthermore, the block size will be randomised to prevent prediction of the next assignment. The study will be blinded to the patient, investigator, treating team, consultants, analyst and to all study personnel with the exception of the research pharmacist.

Duration of treatment and study endpoints

Current guidelines recommend a treatment duration of 14–21 days [15 18]; therefore, treatment will be for no less than 14 total days of any form of TMP-SMX unless alternative therapy is required and no more than 21 days of study drug.

The primary study endpoint is the composite of change of treatment, new mechanical ventilation, or death by day 21. Day 1 is considered the first day of TMP-SMX; hence day 21 represents 20 calendar days afterwards. New mechanical ventilation by day 21 is defined as the necessary use of invasive or non-invasive mechanical ventilation as decided by the patient's clinical treating team. Change in treatment will be specifically defined as dose-escalation due to inefficacy, dose-reduction due to grades 3 and 4 toxicity or switch to a non TMP-SMX PJP treatment due to inefficacy or grades 3 and 4 toxicities. Inefficacy is based on the clinical opinion of the treating team who will make any change while blinded. If a dose escalation or decrease is required, the treating physician or team will be required to commit to an increase or decrease of dose prior to unblinding. At this time, the primary outcome will be met. The decision to initiate any additional therapy will be left to the treating team. All therapeutic decisions will be analysed.

This study has nine secondary clinical efficacy and safety endpoints to be met by day 21. The secondary outcomes are presented in box 3. We will assess for quality of life at Day 28 using the EQ-5D-5L + VAS[55] as well as all-cause mortality and recurrence of PJP infection by days 28, 56 and 90 as a tertiary outcomes of interest.

Follow-up and assessment of study endpoints

Once randomised, every participant will be followed for 90 days from the beginning of treatment and all outcome events will be recorded. At enrolment, demographic characteristics, data on comorbidities and values of baseline complete blood count (CBC), creatinine, electrolytes, blood glucose, liver enzymes (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin), albumin, International Normalized Ratio (INR), prothrombin time (PT), partial thromboplastin time

Box 3 Secondary outcomes (grading based on common terminology criteria for adverse events)

After enrolment and by day 21:

a. Proportion of patients with each of the components of the composite outcome.
b. Proportion of patients requiring oxygen (days 7, 14, 21).
c. Proportion with new use of non-invasive ventilation (eg, Optiflow, Bilevel Positive Airway Pressure or BiPAP).
d. Proportion with grade 3 or 4 renal failure, respectively; and modified Kidney Disease; Imrpving Global Outcomes [KDIGO].[a]
e. Proportion with grade 3 or 4 hyperkalaemia (non-haemolysed sample), respectively.
f. Proportion with grade 3 or 4 drug-induced hepatitis, respectively.
g. Proportion with development of a grade 3 or 4 skin rash, respectively, that was intolerable to the patient, persisted unabated for 48 hours or more, or had bullae or mucous-membrane involvement.
h. Proportion with development of new grade 3 or 4 cytopenias, respectively.
i. Proportion with greater than three episodes of documented capillary or blood hypoglycaemia ≤2.5 mmol/L) (grade 4 adverse event).

[a]We will use modified KDIGO guidelines, wherein acute kidney injury will be defined as: Increase in serum creatinine by ≥26.5 umol/L within 48 hours; or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or new initiation of haemodialysis.

(PTT), lactate dehydrogenase and arterial blood gas (if available) will be collected. Additionally, we will collect data of concomitant opportunistic infections and corresponding treatment.

Patients will be followed daily while admitted to hospital with follow-up blood testing for the development of primary and secondary outcomes. The frequency of follow-up bloodwork will be at the discretion of the treating team in keeping with the standard of care,[56] but will include at least twice weekly tests of CBC, electrolytes, creatinine and liver enzymes. If the patient is well enough for discharge prior to day 21, they will be seen post-discharge in the ID clinic around 21 days as is the current standard practice. Out of hospital follow-up visits will occur at 28, 56 and 90 days by telephone, video conference, email or text-message for the assessment of tertiary outcome. Consent for electronic follow-up using electronic medical records and regional data will be obtained. Table 2 shows the schedule of study visits.

Adverse event categorisation

Safety will be investigated as secondary outcomes of interest, as described above. All grades 3 and 4 ADEs[57] will be validated and categorised for severity and relatedness by a clinical events committee, comprised of three expert clinicians independent of the study team. The following ADE definition will be used: an unfavourable and unintended sign, symptom or disease temporally associated with the use of TMP-SMX, regardless of whether it is considered related to the medical treatment. Relatedness categories will include: (A) Not related: If another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event. (B) Possibly related: If the event follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors. (C) Related: The ADE is clearly related to the study procedures. Any events that are unexpected (in terms of severity or frequency) and related to the study drug will be reported to the REB and Health Canada as required.

Statistical considerations

Sample size

The primary effectiveness endpoint for this study is a composite of death, new mechanical ventilation or

Table 2 Description of study visits and procedures

Assessment	Method	Screening	Baseline	Days 1–21*	Days 28, 56 and 90*
Demographic data	Medical records†	x	x		
Clinical data (eg, vital signs, adverse events)	Medical records†, telephone/video/ email/ text follow-up		x	x	
Respiratory specimens from induced sputum or BAL fluid	Microbiology Lab	x			
Ultrasounds or CT scans or other imaging	Medical records†	x			
Blood tests (eg, liver tests)	Medical records†		x	x	
Quality of life	EQ-5D-5L+VAS				Day 28
Recurrence	Medical records†, telephone/video/ email/ text follow-up				x
Survival	Medical records†, telephone/video/ email/ text follow-up				x

*Time from commencement of treatment with TMP-SMX.
†May include hospital or provincial medical records.
BAL, bronchoalveolar lavage; TMP-SMX, trimethoprim-sulfamethoxazole; VAS, Visual Analogue Scale.

change in treatment by day 21. In accordance with our meta-analysis, 20% of patients on conventional dose of TMP-SMX experienced death.[49] Various published studies have shown estimates varying from 14%[58] to 30%[59] on this dose requiring mechanical ventilation. Conversely, a meta-analysis showed mortality of 9% among the low-dose treatment group.[49] Estimates of mechanical ventilation are sparse in the low-dose group; between 0%[58] and 34%.[60] An observational study of 104 patients reported an Intensive Care Unit admission rate (with and without mechanical ventilation) of 17% in a low-dose group.[32] Therefore, based on unpublished data collected at the MUHC, our meta-analysis, and previously published observational studies and RCTs, we estimate that the composite endpoint will occur in approximately 40% of patients administered the standard dose and 20%–25% of those taking reduced dose. To detect an absolute difference of 15% in event rate (40% in the standard dose group vs 25% in the reduced dose group) with 80% power and a two-tailed alpha error probability of 0.05, we will require a total sample size of 300 participants (n=150 per arm) to obtain an objective of superiority. We have an interest in establishing non-inferiority should a superiority trial fail to detect a significant difference between dosage groups.[61] We will prespecify a prospectively defined margin of 5% for non-inferiority. Assuming there is a true difference in favour of the reduced dose treatment of 9% (eg, 40% vs 31%), a total of 288 (n=144 per arm) patients will be required for 80% power to ensure that the upper limit of a one-sided 95% CI will exclude a difference in favour of the high dose group of more than 5%.

Main analyses

Analysis will be performed according to the intention-to-treat principle. As per the Consolidated Standards of Reporting Trials 2010 guidelines, we will also report a per protocol analysis.[62] Our per protocol definition includes participants who received at least 48 hour of treatment in the assigned study arm. Baseline data will be compared between groups using χ^2 tests, Fisher's exact tests or t-tests, as appropriate. Binary primary and secondary outcomes between groups will be compared using logistic regression adjusting for stratification and presented with 95% CIs.[63] Secondary outcomes will not be multiplicity corrected; however, we will be clear about this as a limitation.

Interim analysis will be performed at 25% and 50% completion and presented to a data safety monitoring board. We will use prespecified rules for stopping the study while accounting for appropriate alpha-spending using the O'Brien-Fleming approach (25% p<0.00001473; 50% p<0.003036; 100% p<0.04695).[64 65] At the 50% point, the sample size may be readjusted based on pooled event rates.[64] Additionally, a non-binding futility analysis will be presented based on recruitment rates and the conditional probability for demonstrating the outcome.

Subgroup analyses

We will conduct preplanned subgroup analyses looking at: age (<50; 50–65; >65), severity of illness, biological sex, HIV versus non-HIV, proven versus presumptive diagnosis and by creatinine clearance (≤15; 16–30; >30). For renal function, drug exposure varies based on creatinine clearance and this could both augment the treatment effect for low dose at reduced eGFR and alter the risk of toxicity. Other subgroup analyses will examine important groups that have been underrepresented in previous trials (eg, age >40, women, non-HIV immunosuppressed). Subgroup analyses will be presented as forest plots with 95% CIs and will conform to the New England Journal of Medicine's guidelines for reporting subgroups.[66]

Missing data

We will consider three scenarios for handling missing data.[67] A definitive choice will be made in consultation with the biostatistician after examination of the degree and pattern of missingness. First, we will consider excluding participants with missing outcome data; we expect that this method may lead to biased estimates and loss of power and will only be chosen if there is minimal missing data. Second, we will consider nearest-neighbour imputation. The missing value will be replaced by a value obtained from the average of measured values from several related in the cohort. Third, we will consider multiple imputation[68] based on the following predictors: age, sex, study arm, HIV-status, type of immunosuppression and comorbidities.

Data safety monitoring board

The data safety monitoring board will be composed of individuals who are independent of the study team and have expertise in disciplines related to the field of the study; these include infectious disease, respirology, nephrology, and epidemiology and biostatistics. Bias of the members will be minimised by blinding to participants and treating centre when reviewing study data. This board shall provide recommendations regarding stopping/continuing enrolment in the study as well as carrying out planned interim analyses.

Patient and public involvement

Patients were not explicitly involved in the design of this protocol; however, patient-important outcome, notably quality of life, was included as a major study outcome. Published results of the trial will be disseminated to study participants via email. Furthermore, study personnel will engage directly with patients at every stage of the trial.

Ethics and dissemination

The study is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent will be given by all patients prior to participating in the study. This protocol and informed consent forms will be reviewed and approved by research ethics board (REB) of each participating site and provided with the publication of the trial results. Confidentiality requirements of each institutional REB will be adhered to. Conditional approval was granted by the MUHC REB on 14 June 2022.

Results of the study will be published in a peer-reviewed journal and presented at international Infectious Diseases and Respirology conferences.

DISCUSSION

While TMP-SMX is the standard of care for PJP, the current guideline recommended dosing may be excessive and associated with toxicity when applied to the modern-day epidemiology of patients with PJP infection. Based on our prior meta-analysis,[49] we seek to re-evaluate the ideal dosing of TMP-SMX. Our phase III randomised, placebo-controlled trial evaluating the efficacy and safety of low dose (10 mg/kg/day of TMP) compared with the standard-of-care (15 mg/kg/day) for the primary outcome of death, new mechanical ventilation, and change in treatment promises to offer a therapeutic strategy that will minimise failure and toxicity and increase the cure rate of this neglected disease.

Our group has the necessary trial infrastructure, experience, requisite number of sites, case numbers and investigators to address this important clinical question, having brought together over a dozen multidisciplinary specialists in PJP from across Canada. With a superiority design we will be adequately powered to demonstrate both improved safety and equivalent treatment efficacy for lower-dose TMP-SMX. We hope to demonstrate that the selected lower dose of TMP-SMX is equally effective at curing PJP (prevention of critical care, death) and furthermore should help limit many of the treatment limiting side effects (serious grades 3 and 4 ADEs) that are more prevalent at higher doses. The trial will be more representative and will include a greater number of women, older adults, people with solid-organ transplant and those with polypharmacy compared with historical PJP treatment trials. The findings of our trial will have far-reaching consequences for clinical practice worldwide given multiple professional society guidelines currently recommend a higher dose of TMP-SMX, however, based on very little evidence. Our findings, therefore, could affect the global management of PJP with important implications for hundreds of thousands of patients treated for the disease every year.

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Contributors ZNS, GB-L, EM and TCL conceived the idea for this trial and wrote the manuscript. AA, SB, AB, AC, MC, BC, CTTC, NE, DG, AJ, KK, AL, VL, SL, DM, MM, LP, SQ, VR, BR, IS, MS, RS, DT and ET provided input on study design, conduct, and plan for data analysis. All coauthors critically revised the protocol for intellectual content and edited the final manuscript.

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