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STUDY PROTOCOL

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A study protocol for a multi-country cluster randomized controlled trial of the impact of a multi-component One Health strategy to eliminate *Opisthorchis viverrini* and soil transmitted helminths in the Lower Mekong Basin

Mary Lorraine Mationg[1,2*], Archie C. A. Clements[3], Gail M. Williams[4], Matthew Kelly[1], Donald E. Stewart[5], Catherine A. Gordon[2], Kinley Wangdi[6], Sirikachorn Tangkawattana[7], Apiporn T. Suwannatrai[8], Vanathom Savathdy[9], Visal Khieu[10], Sangduan Wannachart[11], Suji Yoo O'Connor[1], Simon Forsyth[4], Sean Gannon[2], Peter Odermatt[11,12], Donald P. McManus[2], Somphou Sayasone[9†], Virak Khieu[10†], Banchob Sripa[8†] and Darren J. Gray[2†]

Abstract

Background *Opisthorchis viverrini* (OV) and soil-transmitted helminths (STH) are two of the most common helminths contributing to the Neglected Tropical Disease (NTDs) burden in the Lower Mekong Basin. Although mass drug administration is the cornerstone of control programs to reduce morbidity caused by these infections, this approach has limitations in preventing re-infections. Elimination requires additional measures such as reservoir host treatment, improved hygiene and health education to reinforce MDA's impact. This study aims to examine the impact of a scalable multi-component One Health Helminth Elimination program in the Lower Mekong Basin (HELM) that combines human praziquantel (PZQ) and albendazole (ALB) treatment with a program that includes the "*Magic Glasses*" and the "*Lawa Model*" interventions with health promotion at their core.

Methods This study will employ a cluster randomized controlled trial (cRCT) in 18 rural communities (with sub-district or villages as cluster units) across Cambodia, Laos and Thailand. The control arm will receive one round of PZQ/ALB treatment, while in the intervention arm, multi-component HELM program will be implemented, which includes PZQ/ALB treatment together with the Magic Glasses and Lawa Model interventions. OV and STH infections levels will be evaluated in individuals aged 5–75 years at baseline and will be repeated at follow-up (12 months after the HELM intervention), using modified formalin ethyl-acetate concentration technique and quantitative PCR. The primary

†Somphou Sayasone, Virak Khieu, Banchob Sripa and Darren J. Gray are joint senior authors.

*Correspondence:
Mary Lorraine Mationg
mary.mationg@anu.edu.au; MaryLorraine.Mationg@qimrberghofer.edu.au
Full list of author information is available at the end of the article

outcome of the study will be cumulative incidence of human OV and STH infections. Outcomes between the study arms will be compared using generalized linear mixed models, accounting for clustering.

Discussion Evidence from this trial will quantify the impact of a multi-component One Health control strategy in interrupting Ov and STH infections in the Lower Mekong Basin.

Trial registration Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12622000353796. Prospectively registered 28 February 2022.

Keywords Lawa Model, Magic Glasses, Health education, Mass drug administration, *Opisthorchis viverrini*, Soil-transmitted helminths, Integrated control, Randomized controlled trial

Introduction

Neglected tropical diseases (NTDs) are groups of infectious diseases endemic in tropical regions that thrive among people who are living in impoverished communities [1]. Two helminth-related NTDs that are affecting large population are soil-transmitted helminths (STH) and *Opisthorchis viverrini* (OV) [1, 2]. STH, which includes roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*) and hookworms (*Necator americanus and Anyclostoma duodenale*), infect more than 908.5 million people globally [2]. OV, on the other hand, is widely prevalent in Southeast Asia only, with more than 12.39 million people infected [3].

These infections have major health impacts, causing physical disability, particularly for children, as a result of anaemia [4], malnutrition [5] and stunted growth [6]. OV is classified as a Group one biological carcinogen by the World Health Organization (WHO), the same category as human papillomavirus and hepatitis C virus, for its role in the pathogenesis of cholangiocarcinoma (CCA) [7]. In addition to their adverse effect on physical health, these two NTDs also contribute to the continuation of poverty and impede socio-economic development—poor communities are disproportionately affected as infections are driven by inadequate sanitation and hygiene, and a lack of clean water [8–11].

Thailand, Cambodia and Lao PDR are among the countries in the Lower Mekong Basin with ongoing STH and OV transmission and are in different stages towards elimination. In terms of STH control, Thailand has generally lower infection levels than Cambodia and Lao PDR, with prevalence in endemic areas in the northeast region only up to 4% and in the south only up to 11% [12–16], compared to Cambodia [17–20] and Lao PDR [21–29] which both exceed 40% prevalence in many endemic areas. For OV, despite decades of control in Thailand, prevalence of infection remains above 15% in some provinces in northeast Thailand, and this prevalence disguises substantial community-level variation [30]. Despite this, Thailand is also much further along the road to elimination for OV than Cambodia, which has a prevalence of > 40% in some endemic areas [31, 32], and Lao PDR, which has a national OV prevalence of 35% [33]. Khon Kaen Province in northeast Thailand is an illustrative example of the exceptionally high CCA incidence rates in areas with high OV prevalence, with an incidence rate of 27.81 cases per 100,000 person-years in 2018 [34]. In contrast, the USA has an incidence rate of 1.2 per 100,000 person-years [35]. CCA is a highly lethal cancer, with Thai patients having a 5-year overall survival of just 10% [34], and OV infection has been demonstrated to be a key risk factor for the development of CCA [7].

Persistent mass drug administration (MDA), the regular treatment with anti-helminthic drugs of entire (sub-) populations in at-risk communities in endemic regions, is currently the primary control strategy for STH and OV [36]. The drugs of choice for MDA programs are albendazole (ALB) or mebendazole for STH infections and praziquantel (PZQ) for OV. The current WHO strategy for STH is to continually treat pre-school and school-age children, women of childbearing age and adults at high risk once or twice per year depending on prevalence [36]. The WHO recommends annual universal MDA for OV control in communities where the prevalence of OV exceeds 20% and biennially in areas where prevalence is less than 20% [37, 38]. These methods are effective in achieving morbidity control; however, they do not prevent re-infection and prevalence quickly increases to between 57% (hookworm) and 94% (roundworm) of pre-treatment levels within 6–12 months of treatment being stopped [39]. Rapid OV re-infection after successful PZQ treatment has also been reported with re-infection rates as high as 90% within 1 year [40–42].

Of concern are the many examples of drug resistance developing against nematodes of sheep and other livestock as a result of continued MDA [43], and it is believed that, given the selection pressure that MDA exerts, the development of widespread drug resistance in species that infect humans is a plausible threat [39, 44–46]. Several studies have also shown significant association between the frequency of PZQ treatment and OV reinfection [47–49]. Repeated PZQ treatment has shown to

create complacency around the dietary practice of consuming raw freshwater fish and has also been linked to increased risk of CCA [50].

We posit that interventions preventing re-infection (such as health education to reduce risky behaviours and reduction of environmental contamination through animal pharmacotherapy) are required to augment MDA as part of an integrated approach, thus limiting the number of treatment cycles required for effective control. More efficient use of anti-helminthic drugs will reduce the selection pressure favouring drug-resistant organisms, leading to a more sustainable long-term control strategy with the prospect of transmission interruption for these highly prevalent diseases in the Lower Mekong Basin.

Here we present the design and rationale for the Helminth Elimination in the Lower Mekong Basin (HELM) trial, a cluster randomised control trial (cRCT) that aims to evaluate the effectiveness of combining the human PZQ/ALB treatment with a multi-component elimination program, that includes the *Magic Glasses* and the *Lawa Model*, compared to human PZQ/ALB treatment alone for the control of OV and STH. This study will contribute to the existing knowledge base by testing the impact of two interventions which have previously shown to be effective in reducing the prevalence of helminth infections. More specifically, the *Magic Glasses* intervention is health education cartoon for the prevention of STH infection in schoolchildren and has been shown to be effective for increasing knowledge, attitudes and behaviour, and reducing STH prevalence in China and the Philippines [51, 52], but has not been tested for reducing the prevalence of OV infections in a Lower Mekong basin context. The *Lawa Model* intervention employs an EcoHealth/One Health approach comprising human and feline PZQ treatment, novel intensive health education methods (particularly around diet behaviour change) both in the communities and in schools, ecosystem monitoring and active community participation [53]. It has been shown to be effective in reducing OV prevalence (from 60% to less than 10%) in an uncontrolled pre-post study of Northeastern Thailand villages [53], but has not yet been generalized to Cambodian and Lao PDR contexts or tested using a cRCT design.

This study represents the first report, to our knowledge, of a cRCT involving multiple diseases with multiple interventions based on a One Health approach across multiple countries in the Lower Mekong Basin. This research effort is in line with the 2021–2030 WHO NTD control roadmap which emphasizes integrated management in the control of several NTDs to sustain and build on the success of previous control efforts [1]. The results of this study will inform the development of scalable public health strategies to control STH and OV infections, thus contributing to the ultimate goal of effective and sustainable STH and OV control programs in the Lower Mekong Basin. The trial reported here is a collaborative project of institutions across Australia, Cambodia, Laos, Thailand, Switzerland and the UK.

Methods

This study protocol has been prepared according to the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines [54, 55]. A checklist of recommended protocol components is provided in supplementary file 1.

Study design and setting

This study will employ an open label pair-matched cRCT to evaluate the impact of combining PZQ/ALB treatment with a multi-component elimination programme that comprises the *Magic Glasses* and the *Lawa Model* compared to PZQ/ALB treatment alone in the Lower Mekong Basin. The trial will be conducted in three locations: Chhaeb District in Preah Vihear Province (Cambodia), Champhone District in Savannakhet Province (Lao PDR) and Chonnabot District in Khon Kaen Province (Thailand) that are co-endemic for opisthorchiasis and STH. Infection prevalence in these sentinel sites ranges from 30 to 80% for OV and 30 to 60% for STH (personal communication with the local investigators in each country).

For Cambodia and Lao PDR, the study cluster will be the villages. Eight villages for each country will be selected and matched into pairs based on human population size, OV/STH prevalence and factors related to OV/STH transmission such as distance to water source, and latrine coverage to reduce confounding and to increase statistical efficiency. A buffer zone of 3-km radius will be applied to separate the clusters from one another and thereby reduce contamination. One village of each pair will be randomly assigned as the intervention arm of the study leaving the remaining as the control. For Thailand, the study clusters will be sub-districts. Two sub-districts will be randomly allocated to either the intervention or control arm. The randomization is generated by the study team using the RAND function in Microsoft excel (Microsoft 365). The allocation will be the same across the duration of the study.

In each cluster, a fixed sentinel cohort of people will be selected and will be followed up over 1 year. Parasitological assessment, knowledge, attitudes and practices (KAP) survey will be carried out in both study arms at baseline and will be repeated at follow-up. Following the baseline procedures, the intervention arm will receive the HELM programme while the control arm will receive human PZQ/ALB treatment only. For ethical reasons and key for mobilization of the study population, clusters in

the control arm will receive the HELM intervention at the end of the trial. In addition to the human procedures, animal (cat, dog and fish) surveys will be conducted at baseline and will be implemented again at follow-up. The follow-up surveys will be implemented 12 months after the delivery of the HELM intervention. Treatment of animals (cats and dogs) in the intervention arm will be conducted after the baseline survey and will be implemented 6 and 12 months later. Animals in the control arm will remain untreated throughout the study, with treatment provided upon conclusion of the study. Figure 1 depicts the trial profile and Fig. 2 shows the SPIRIT figure.

Study population

The participants for this study will be people aged 5 to 75 years old. People who provide informed consent, who had resided in the study area for more than 12 months, and who will continue to live in the study area over the study period will be included. Temporary and migrating residents will be excluded.

Sample size

Because STH infections are less prevalent than OV infections in the study region, the decision was made to base the sample size calculations on the predicted STH prevalence. This approach increases the power of detecting an effect when the cumulative incidences of STH and OV infections are combined. Based upon regional STH prevalence data [17, 26], a design effect of four was assumed. Using the conventional thresholds of $\alpha = 0.05$ and power > 80%, a sample size of $N = 4800$ at the end of the trial will be required to detect an effect as low as a 30% relative difference, assuming a combined cumulative incidence of at least 25% in the control group. In order to account for 20% attrition of participants, a sentinel cohort of $N = 6000$ across nine cluster pairs ($N = 350$/cluster) will be recruited.

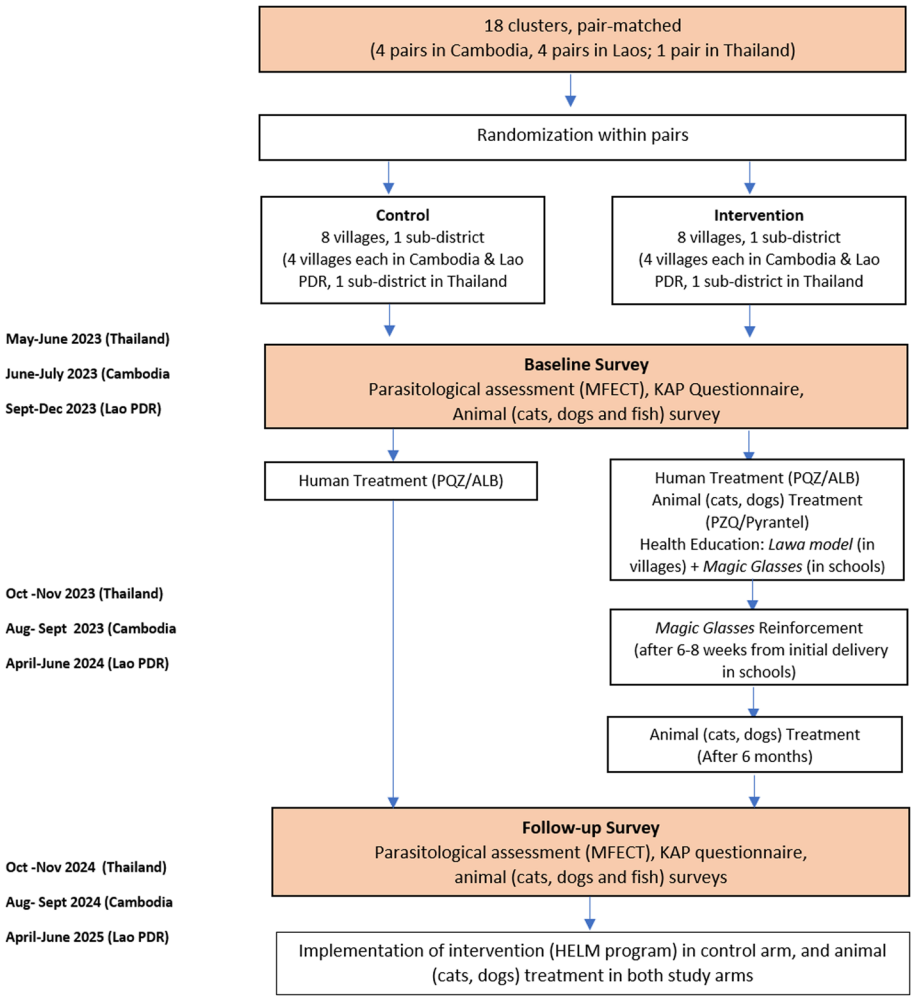

Fig. 1 HELM trial profile

	Enrolment	Allocation	STUDY PERIOD												
			Post-allocation (months)												Close-out
TIMEPOINT	-T1	T0	T_1												T_2
Months		0	1	2	3	4	5	6	7	8	9	10	11	12	13
ENROLMENT:															
Eligibility screening	X														
Informed consent	X														
Baseline assessment	X														
Allocation		X													
INTERVENTIONS:															
Magic Glasses in schools			X		X										
Community Health Education			X												
Human Albendazole and Praziquantel treatment			X												X
Animal Treatment (cats and dogs in the community)			X						X						X
ASSESSMENTS:															
OV and STH infection status (humans)	X														X
Knowledge, attitude, practices	X														X
OV and STH infection status (animals)	X														X

Fig. 2 SPIRIT figure—schedule of enrolment, interventions and assessments

Blinding

Since the study village intervention status cannot be masked due to the nature of the intervention, the study participants, research staff and health village volunteers cannot be blinded to the study group allocation. However, laboratory technologist (as primary outcome assessors) will be blinded to the intervention status. The analysis of the trial result will be performed by the study team; because of this, blinding of the study group allocation is not feasible.

Intervention

The HELM program is a multi-component integrated One Health strategy adapting the two successful public health interventions, the *Magic Glasses* and the *Lawa Model*. The components of this program include school and community-based health and hygiene education, human (ALB/PZQ) and animal treatment (Pyrantel/PZQ).

Magic glasses

For the current study, two animated health-education cartoons will be developed, one targeting STH (*Magic Glasses Lower Mekong* (MGLM)) and the other targeting OV (*Magic Glasses Opisthorchiasis* (MGO)). Briefly, the new animated cartoons will be adapted from the previous *Magic Glasses* and informed by literature reviews on risk factors and KAP associated with STH and OV in the Lower Mekong region. The Thai version of the cartoon will be initially developed then modified for Cambodia and Lao PDR to incorporate culturally appropriate local attire and languages. Conforming to the previous Magic Glasses [51, 52], to ensure that the health messages in the cartoons will be both engaging and educational, behavioural theories such as the Health Belief Model, Integrated Behavioural Model and Social Cognitive Theory will be applied. The cartoons will be developed by 2D animation company, an animation company based in Khon Kaen, Thailand. Six cartoons (two cartoons for each country) will be produced in total. The audio for the cartoons will be dubbed and recorded by local voice actors in each country.

In all countries, the delivery of the MGO and MGM in schools linked to the intervention clusters will be implemented either before or after the community health education. Each package will comprise the cartoon (accompanied by a classroom discussion), distribution of pamphlets (containing the key messages from the cartoon), a drawing competition and an essay writing competition. To reinforce the messages, the cartoons will be shown again in the schools 6–8 weeks after the initial delivery.

Lawa model

For this trial, the core components of the *Lawa Model* for community health education targeting OV will be replicated for Thailand while adapted and scaled up according to the local service set-up for Cambodia and Lao PDR.

The OV information, education and communication (IEC) materials used in the *Lawa Model* will be utilized as reference in the development of the OV brochure and billboard for the main trial. IEC materials will be also developed for STH. The IEC materials for STH and OV will be initially developed in English, then translated to the local language of each country. All country sites will be consulted to ensure the IEC materials are socially and culturally appropriate.

For Thailand, community health education will comprise the kick-off ceremony to activate the community, cooking shows, door-to-door health education, twilight health education (lectures on STH and OV), public broadcasts of OV educational folk songs in the community and installation of billboards containing STH and OV-related images and messaging. The delivery of the intervention will be implemented for 2 weeks by the research staff and/or trained village volunteers.

For Cambodia, the community health education will include a series of STH and OV lectures delivered by the trained research staff and/or village volunteers twice a week for 2 weeks. Each lecture will be supplemented by STH or OV brochure distribution and a cooking class after the OV lecture. To educate those who did not attend the lectures, the research staff will conduct door-to-door health education alongside the PZQ and ALB MDA delivery. Billboards will be installed in several strategic locations in each village.

For Lao PDR, the community health education will also include a series of STH and OV lectures to be delivered by trained research staff and/or village volunteers twice a week for 2 weeks. The activities will also include distribution of STH and OV brochures after each lecture, a cooking class after the OV lecture and installation of STH and OV billboards.

Human treatment

PZQ (40 mg/kg body weight) and ALB (400 mg) will be the deworming drugs used for OV and STH, respectively. These drugs are safe for use, recommended by WHO [36, 37], and used by the control programs in each country. The MDA in both the study arms will occur simultaneously within the delivery of the community health education.

In Thailand, in line with the local treatment guidelines for OV and STH, targeted treatment will be implemented in both study arms. Only those infected with OV and STH will be treated with PZQ and ALB, respectively. In Cambodia, in both study arms, drugs will be distributed to all residents aged > 5 years for PZQ and aged ≥ 5 years for ALB. These doses will be taken under direct observation by the research team. To avoid side effects of the drugs, all participants will be provided with a meal prior to treatment. The participants will be monitored for a few minutes after the taking the medicine. They will be advised to attend the local health station or contact the research team if they are unwell after the drug distribution. As the research team will be available in the study area for several days after the treatment, passive monitoring of adverse events will be undertaken.

In Lao PDR, the PZQ MDA will be done in the community, targeting residents aged > 5 years. For ALB MDA, all residents (aged ≥ 5 years) will be treated in the community except children attending the primary schools linked to the study villages. They will receive the recommended 400 mg dose of ALB as part of the regular Ministry of Health deworming program in schools. Children not treated in schools will be treated in the community. The research team in coordination with members of the Centre for Malaria, Parasitology and Entomology (CMPE) and the Department of Communicable Disease Control (DCDC) will implement the MDA delivery in the community. All doses will be taken under direct observed treatment. Adverse events monitoring will be undertaken over the course of the treatment.

For Thailand, treatment coverage will be collected by noting the number of PZQ and ALB delivered and taken by individuals positive for OV or STH and the total number of individuals positive for OV/STH for each cluster. For Cambodia and Laos, treatment coverage will be documented by recording the number of PZQ and ALB doses delivered and taken by residents at each cluster as well as the total number of residents in each cluster.

Animal treatment

In line with the *Lawa Model*, animal reservoir treatment will also be adapted for this study. The reservoir hosts for OV/STH infections such as cats and dogs can participate in parasite transmission thus, treating them can help interrupt the transmission cycle. For this study, animals in the intervention arm across the three project country sites will be treated with three rounds of PZQ (40 mg/kg) and pyrantel pamoate (10 mg/kg) once orally. The schedule for treatment will be done after the baseline survey, at 6 months (after initial treatment) and 12 months later (after the final follow-up survey). Animals in the control arm will remain untreated throughout the study, with treatment provided upon conclusion of the study.

Data collection

To ensure the trial procedures will be implemented consistently across all the country sites, several workshops will be organized and participated in by the study investigators. Subsequently, standard operating procedures and standardized research data collection tools (questionnaires and forms) will be developed. Local staff in all the

three sites will undertake orientation prior to the conduct of the baseline survey and the study interventions. Only trained local staff will administer the following standardized study procedures including the use of the database developed for the study using the REDCap electronic data capture tools. Quality control of the data will be a routine part of field supervision.

Recruitment and administration of household and KAP questionnaires

The recruitment of study participants will be done through household visits. The local study team from each country will obtain consent from the study participant prior to any specific activities of related to the study. To assess the housing conditions, basic services and economic status of the family, the household interview will be administered to the household head. After the household interview, all the household members aged ≥ 5 years will be invited to participate in the study. After securing informed consent from each participant, the KAP questionnaire will be administered. The KAP questionnaire will include sections eliciting details on demographics, medical history, knowledge, attitude and practices related to STH and OV. The questionnaire will be translated and delivered to the local language of each country. The survey team will be trained on the use of Android-based tablets running the REDCap electronic data capture tool to administer the survey questionnaires and collect geographic coordinates at each selected household. During the data collection, data issues will be identified and addressed on daily basis.

Stool sample collection and laboratory procedures

One stool sample (around 10–15 g) will be requested from each participant as part of their participation in the trial. They will be instructed on how to collect the sample and provided with a stool collection kit that includes a stool container, gloves and applicator stick. Furthermore, they will be asked to collect the sample the next morning. The research team will allot 2–3 days for stool collection visits per household to ensure high submission rates. After collection, the research team will immediately process the samples in the field, preserving a 2-g aliquot in 10 ml of 10% formalin for modified Formalin ethyl-acetate concentration technique (MFECT) [56], a 3-g aliquot fresh sample to be frozen and a 3-g aliquot in 80% ethanol for molecular analysis employing quantitative polymerase chain reaction (qPCR) for the diagnosis of STH and OV. Frozen samples will be kept at − 20 °C and will be stored in dry ice during transport. Samples for MFECT and molecular analysis will be kept chilled until transported to the designated laboratory in each country (CNM in Phnom Penh, KKU in Thailand and TPHI in Lao PDR), and then examined using MFECT. Preserved stool samples for molecular analysis will be performed either in Khon Kaen University, Thailand or QIMR Berghofer Medical Research Institute, Australia.

Participant retention plan

Progress of the study will be communicated to and discussed with the local stakeholders including the health officials of each study village. To ensure participation at follow-up, all study participants will be provided with a reminder of their 12-month follow-up assessments a week before the scheduled visit through the village chief and health workers. During the follow-up assessments, several household visits will be scheduled to have higher possibility of covering all study participants.

Provision of post-trial care

There is no anticipated harm and compensation for trial participation. Any person found positive for OV or STH infection at follow-up will be referred to the local health authorities for clinical care and treatment.

Animal survey

Stool samples will be collected from domestic cats and dogs of the households enrolled in both study arms. The conduct of the baseline survey will either be completed alongside or after the human survey. Consent from the animal owner will be obtained prior to stool collection. All animals will be examined physically before sample collection. Animals that are either young (puppies less than 3 weeks old or kitten less than 6 months old), pregnant, lactating or ill will be excluded from the study. The stool sample collected after applying the enema will be immediately processed in the field and 3 aliquots will be preserved for MFECT (2-g aliquot in 10 ml of 10% formalin), molecular analysis (3-g aliquot in 80% ethanol) and 3-g fresh frozen sample. Stool examination by MFECT will be conducted at a designated laboratory at each site. Preserved stool samples for molecular analysis will be performed either at Khon Kaen University, Thailand, or QIMR Berghofer Medical Research Institute, Australia. The follow-up survey will be repeated across the three country sites after 12 months.

Fish survey

To confirm the presence of OV in fish, fish will be purchased from the fisherfolk at the local pond/lake in the study area by the research staff. If there is no local water source in the study villages, the residents will be interviewed on which source they normally buy their fish from. The fish sellers will be asked about the sources of fish and the type of water body (e.g. rivers, ponds/lakes and dams). Fish purchased in the field will be stored at

4 °C and transported to designated laboratories in each country. Each fish will be identified using a using a freshwater fish key (https://www.fishbase.de/), weighed and measured. OV from each fish will be identified either by the digestion [57] or compression [58] method, or both.

Data management and confidentiality

Baseline survey data will be collected in-field by the research team on electronic tablets using REDCap electronic data capture tools [59, 60]. For Cambodia and Lao PDR, due to internet connectivity issues in the study areas, data will be collected offline and will be sent to the server daily using a secure wireless connection. For Thailand, the data will be collected online. Follow-up survey and microscopy data will be similarly captured using REDCap tools. The REDCap database is hosted at the University of Queensland and data will be stored for 5 years from the date of the data collection, after which the de-identified data will be archived. Data quality will be assured through the use of data validation settings in REDCap and continuous monitoring and feedback by study investigators.

All information that will be collected from the study participants will be kept confidential. Stool samples will be labeled using each participant's assigned ID, with no identifying information. Reports that will be generated from this study will only contain summary of the data collection without the names of the respondents. The final study datasets will be accessible only to the study investigators.

Study outcomes and statistical analysis

To assess the primary and secondary outcomes of this trial, the final cohort will be restricted to [1] participants with a stool sample tested at baseline and follow-up and [2] those who completed a KAP questionnaire at baseline and follow-up, respectively. The primary outcome of the study will be cumulative incidence of human OV and STH infection. Prevalence of infection in humans and mean infection intensity, both with corresponding 95% confidence intervals, will be calculated from the baseline survey data. Exploratory analysis of variables that are potentially associated with the outcome (e.g. age, sex, occupation) will be conducted on the baseline data. Multivariate regression will be used for formal analyses of follow-up incidence (log-binomial model) and intensity of infection (negative binomial model). Covariates will include baseline infection and other relevant covariates selected from preliminary analyses.

Two multi-level models (i.e. combined (all three countries) and stratified by country), with village as a random effect, will be applied using SAS (r) Proprietary Software 9.4 (TS1M7) [Copyright (c) 2016 by SAS Institute Inc., Cary, NC, USA, Licensed to Queensland Institute of Medical Research (QIMR)- Genetics and Population Health, Site 10,008,492. software [61]. Relative risk estimates will be converted to estimates of control program effectiveness against any helminth, STH and OV infection, separately. Sub-group analysis may be undertaken to evaluate intervention effect with baseline prevalence and infection intensity.

The secondary outcome of the study will be the change in knowledge, attitude and behaviour measured by a KAP questionnaire. The scores for the knowledge, attitude and behaviour components in the KAP questionnaire will be calculated as percentages, and differences between groups will be expressed in percentages points. Two multi-level models (i.e. combined (all three countries) and stratified by country), with village as a random effect, will also be developed using linear regression. Animal host (e.g. cats, dogs and fish) data will be summarized descriptively in terms of prevalence and infection density.

Interim analyses

This study is classified as a low-risk interventional trial. Therefore, it is deemed not necessary to plan an interim analysis for patient safety reasons.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

This trial will be overseen by the chief principal investigator (PI) who will be responsible for providing guidance and technical assistance to each country site PI and all trial-related activities. The chief PI will ensure that the trial objectives are met according to the study timelines and protocol, including allocation of financial resources for the trial conduct. Country PIs, meanwhile, will be responsible for the recruitment, assessments and intervention implementation. The country PI will also be responsible for the day-to-day supervision of the local study team during the trial activity. Updates from each country site will be provided to the study's chief investigators during regular monthly meetings. The trial steering committee will be comprised by study's chief investigators chaired by the study's principal investigator. Stakeholders of this trial will include Ministries of Health and Education as well as local village health volunteers/workers and village leaders.

Composition of the data monitoring committee

There is no data monitoring committee as minimal risk is associated with this trial.

Adverse event reporting

Given the nature of the study, we do not expect to have adverse events. The topics that will be discussed during the health education sessions are not controversial. The drugs ALB and PZQ used for the treatment of STH and OV, respectively, have been recommended by the WHO and used extensively worldwide with minimal side effects [61]. Most common side effects reported from these drugs include abdominal pain, nausea, vomiting, diarrhoea and fatigue [61]. Monitoring of these side effects is described in the "Human treatment" section above. Serious adverse events (SAEs) are also not anticipated from taking these drugs.

Frequency and plans for auditing trial conduct

The study investigators are responsible for auditing the conduct of the trial. Each country PI and study staff will have regular meetings during the course of the recruitment and data collection. Review of data will be done by the study team on an ongoing basis for completeness and accuracy. Monitoring assessments will be conducted by the principal investigators. Progress and key results will be discussed by the study investigators through feedback meetings or workshops. Any unanticipated problems and protocol deviation that may arise during the study will be documented and reported to the ethics committee.

Dissemination

The trial results will be presented to the Ministry of Health and local stakeholders in each project site. Results will also be presented at international conferences and published in peer-reviewed journals.

Discussion

Control strategies for STH and OV in the past decade tend to centre on MDA. As discussed above, there remains a need for intervention approaches that augment existing MDA strategies to reduce reinfection and eliminate transmission. The HELM trial is one of the first RCTs evaluating the impact of a scalable integrated One Health approach utilizing multiple interventions targeting multiple helminths simultaneously across multiple countries to generate the evidence base to advance the WHO 2030 NTDs roadmap [1]. This trial brings together two known effective interventions for STH (*Magic Glasses* [51, 52] and OV (*Lawa Model* [53]) across multiple countries in the Lower Mekong Basin to form a scalable helminth elimination program. The results from this trial will provide empirical evidence regarding the impact of the multifaceted helminth elimination program in comparison to MDA alone on STH and OV among individuals at risk for these infections.

This trial will make use of spatial analyses to produce robust maps of the distribution of STH and OV infection and risk across the Lower Mekong Basin, which will be critical to geographically guide the implementation of a scaled up version of our elimination program and in ensuring the efficient allocation of scarce resources in the future. Predicted prevalences will be used to inform baseline parameters for modelling the short-, medium- and long-term impacts of the inventions.

To assess the viability of our helminth elimination program overtime, mathematical modelling approaches will be used to simulate the short-, medium- and long-term impacts across various endemicities in the Lower Mekong Basin, for varying efficacy, coverage and sustainability. Furthermore, the cost-effectiveness and feasibility of the multicomponent helminth elimination program will be assessed and used in developing scaling up protocol and guidelines for the roll-out of the helminth elimination program across the endemic regions of the Lower Mekong Basin.

Serious challenges remain in the development of integrated control model that demonstrably bolster reduced STH and OV infection levels. With this current work, we aim to provide robust evidence for policymakers on the most favourable design for STH and OV control strategies. This evidence further offers opportunity to inform future guidelines and recommendations on integrated management of NTDs advocated by WHO [1] and contribute in the development of comprehensive intervention strategy against STH and OV infections in the Lower Mekong Basin.

Trial status

This is an ongoing trial (as date of protocol submission). Protocol version number: Version 2.0, January 2024. Participants were recruited from May 22 to June 20, 2023, in Thailand, June 19–July 6, 2023, in Cambodia and September 28–December 6, 2023, in Lao PDR. The last participant follow-up is expected to be completed in June 2025. Considering the nuances among county sites in terms of development and delivery of the multi-component elimination program, submission of this study protocol was not possible prior to participant enrolment to ensure consistency in reporting of the intervention delivery. This protocol version provides accurate account of the trial design, intervention implementation and study procedures.

Abbreviations

ALB	Albendazole
HELM	Helminth Elimination in the Lower Mekong
MG	Magic Glasses

MDA	Mass Drug Administration
NTDs	Neglected tropical diseases
STH	Soil-transmitted helminths
OV	*Opisthorchis viverrini*
PZQ	Praziquantel
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08616-6.

Supplementary Material 1.

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Authors' contributions
DJG, BS, SS and VK are joint principal investigators. DJG, ACAC, BS, VK, SS, DPM and GMW conceptualized the idea. DJG, ACAC, BS, DPM, GMW, PO, DS, MK, CG, KW secured funding. DJG, ACAC, GMW, DPM, BS, SS, VK, DS, MK, CG and KW contributed to the design of the study. Project Administration: DJG, MLM, BS, SS, VK; Fieldwork: DJG, MLM, BS, SS, VK, SK, AS, VN, SW, VK. Database development: SF and MLM. MLM and DJG and SG drafted the manuscript. All authors contributed to editing and revising the manuscript. All authors read and approved the final manuscript.

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Data availability
The data supporting the findings of this study will be available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was submitted to and received ethical approval from the Australian National University Human Research Ethics Committee (Protocol number 2022/507), Cambodia Ministry of Health National Ethics Committee for Health Research (NECHR) (209NECHR), the Lao PDR Ministry NECHR (07NCEHR) and Khon Kaen University Ethics Committee for Human Research (Reference No. HE651147). This study is prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12622000353796. Participation in the survey will be voluntary. Informed consent will be obtained from all participants ≥ 18 years old. Inclusion of participants < 18 years old required consent from a parent or guardian and assent from individuals 5 to 17 years old. The study objectives, intervention components, voluntary participation and the right to withdraw at any time will be verbally elaborated and outlined in the information sheet. Two copies will be signed by the study participants: an original copy and a duplicate. Researchers will keep the original copies of the consents signed by the study participants and leave the duplicate copies with them for their own records. This trial will also involve collection of stool specimens for storage. If the study participants will not allow the storage and use of remaining stool samples for future research, the remaining samples will be disposed immediately after the completion of all the procedures of this study.
This study also obtained ethical approval from the Australian National University Animal Ethics Committee (Protocol Number A2022/27) and Institutional Animal Care and Use Committee of Khon Kaen University (Reference No. 660201.2.11/245 (39)).

Consent for publication
Not applicable—there are no personal information or identifying images of study participants are presented here or will be presented in reports of the trial results.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia. [2]QIMR Berghofer Medical Research Institute, Brisbane, Australia. [3]Queen's University, Belfast, UK. [4]School of Public Health, University of Queensland, Brisbane, Australia. [5]School of Medicine, Griffith University, Gold Coast, Australia. [6]Canberra University, Canberra, Australia. [7]Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen, Thailand. [8]Department of Tropical Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. [9]Lao Tropical and Public Health Institute, Vientiane, Lao PDR. [10]National Centre for Parasitology, Entomology and Malaria Control, Phnom Penh, Cambodia. [11]Swiss Tropical and Public Health Institute, Basel, Switzerland. [12]University of Basel, Basel, Switzerland.

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