Clinical Trial Protocol

Trial name:

School versus community-based albendazole deworming for control of soil transmitted helminths in school-age children in Vietnam – a cluster randomised controlled trial

Short trial name:

CoDe-STH (Community Deworming against STH) trial

Protocol versions and amendments

Protocol number	Version number	Version date
U1111-1220-0338	Version 1.0	25/01/2019
U1111-1220-0338	Version 2.0	14/05/2019

General Information

Trial sponsor

Name	University of New South Wales
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Trial sponsor authorisation

Title	Name	Email	
Prof	John Kaldor	jkaldor@kirby.unsw.edu.au	

Trial Sites

Site name	Site address
64 primary schools Dak Lak province, Vietnam	Dak Lak province, Vietnam (Primary schools yet to be selected)

Chief Investigator

Title	Name	Email	Address and telephone number
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Study Co-investigators

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Independent and/or trial safety committees

Title	Name	Email
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Funding and resources

This study is funded by the National Health & Medical Research Council, grant number APP1139561

Insurance

Insurance will be provided by the trial sponsor, the University of New South Wales.

Introduction and Background Information

Background information

Soil-transmitted helminths (STH) are parasitic worms that affect more than 1.45 billion people worldwide [1]. They include *Necator americanus* and *Ancylostoma duodenale* (hookworms), *Ascaris lumbricoides* (roundworm) and *Trichuris trichiura* (whipworm). Chronic, intense STH infections contribute to malnutrition and iron-deficiency anaemia, impair physical and cognitive development, and can lead to poor school performance in children, reduced work productivity in adults, and adverse pregnancy outcomes [2,3]. Infection prevalence and intensity typically peaks in school-aged children for *A. lumbricoides* and *T. trichiura*; while hookworm prevalence and intensity generally increase with age, levelling off in adulthood [4]. STH infective stages survive in warm, moist soil, and transmission occurs via ingestion of eggs via the faecal-oral route, or skin contact with hookworm larvae. STH are, therefore, common in poverty-stricken areas with poor sanitation and hygiene [4].

Regular deworming using benzimidazole anthelmintics drugs, albendazole 400mg or mebendazole 500mg, is the main strategy to control STH-associated morbidity [5]. Deworming must be repeated regularly, given that in the absence of adequate sanitation and hygiene, reinfection occurs rapidly [6]. Nevertheless, important benefits are achieved by periodic deworming because it halts negative health consequences associated with chronic infection [7].

Trial rationale

World Health Organization (WHO) guidelines for STH control advocate school-based targeted delivery of albendazole or mebendazole, mainly to school-aged children, once or twice annually [4]. The main justification for this strategy is that school-aged children tend to harbour the highest levels of infection, and consequently are at the highest risk of morbidity [8]. High treatment coverage of school-aged children can be achieved using a school-based approach, provided the school enrolment rate is high or there are mechanisms to include non-enrolled children [8].

However, recent evidence has raised questions about WHO guidelines. Mathematical modelling demonstrates limited impact of school-based targeted deworming on STH transmission, especially hookworm [9,10]. In most settings, adult reservoirs will allow ongoing transmission of both *A. lumbricoides* and hookworm, even if most children are treated, resulting in children being reinfected after treatment [9]. Community-based mass deworming programs, treating the entire population, could reduce transmission more effectively than school-based targeted programs due to substantial reduction in environmental contamination [9,10]. This is further supported by a recent meta-analysis showing greater prevalence reduction of hookworm and *A. lumbricoides* in children following community-wide mass deworming, compared to child-targeted deworming [11]. A pilot study that we conducted in Timor-Leste showed preliminary evidence that community-wide deworming resulted in greater reduction in hookworm prevalence in school-aged children than targeted school-based deworming [12].

To date, no fully-powered field trials have reported a comparison of targeted and mass deworming strategies. This study aims to test the hypothesis that, by eliminating STH reservoirs in adults and other age groups, reinfections in school-aged children will be lower after community-wide deworming, compared to child-targeted deworming.

This study will be conducted in Dak Lak province, Vietnam, where school-based deworming using mebendazole has occurred since 2014 (Nguyen, personal communication). Due to low efficacy of mebendazole against hookworm [13], there remains a substantial burden of hookworm among school-aged children in Dak Lak, with lower prevalence of *A. lumbricoides* and *T. trichiura* [14]. This was confirmed in our preliminary survey conducted in November-December 2018 in 13 schools in Dak Lak province (442 children total). We found an overall hookworm prevalence of 20.6% (range 3.2-55.2), and much lower prevalence of *Ascaris* and *Trichuris* spp.

Trial objective

The objective of this trial is to compare the effectiveness of community-wide mass deworming with albendazole and school-based targeted deworming with albendazole, in terms of reducing STH prevalence in school-aged children. The study will test the hypothesis that, by eliminating reservoirs of infection in adults and others who are not school-aged children, the prevalence of STH among school-aged children will be lower in the community-wide mass deworming arm.

Type of study

Cluster randomised controlled trial

Trial design

A two-arm cluster randomised controlled trial will be conducted in rural communities in Dak Lak province, Vietnam. Each cluster will be a primary school. In the intervention arm of the study, community-based mass deworming will be delivered as the study intervention. This will involve distributing albendazole to all community members (aged over 1 year, excluding pregnant women in the first trimester) using a community-based delivery system. Distribution will occur every 6 months for 12 months. In the control arm of the study, school-based targeted deworming will be delivered. This will involve distributing albendazole to the children attending the primary school (grades 1-5, typically aged 6-11 years). In both study arms, deworming will occur every 6 months for 12 months, at the same time as the government standard school-based deworming program, but will be done by the research team, using albendazole instead of the usual mebendazole.

The primary outcome of the study is hookworm prevalence among school-aged children, measured at the final study follow-up. Secondary outcomes include prevalence of individual hookworm species, prevalence of *Ascaris* and *Trichuris* spp., and infection intensity of each STH species.

Participants in data collection will be school-aged children in grades 1-4. Data collection will include obtaining stool samples to diagnose STH infections, and completing study questionnaires that will be conducted as interviews. Data collection will occur at baseline and at two six-monthly follow-up visits, immediately prior to each round of deworming.

Trial population

There will be two types of participants: those who participate in both the study intervention and data collection, and those who participate in the study intervention only.

Participants in data collection will be school-aged children attending the primary schools participating in the study, who are in grades 1-4 at baseline (aged 6-10 years). There are no specific exclusion criteria. All children who are in grades 1-4 whose parents provide informed consent will be eligible for participation in the study. Grade 5 children will not participate in data collection because they will not be present at the final study follow-up.

Participants in the study intervention (i.e., receiving albendazole) will include school-aged children in both study arms. Additionally, in the intervention arm, participants in the intervention will include all community members (in 2-3 hamlets that send children to the primary school) aged >1 year, excluding pregnant women in the first trimester.

Compliance statement

This trial will be conducted in accordance with this trial protocol at all times.

Investigational product(s)

Product name	Albendazole
Intended use(s)	Distribution in school- and community-wide deworming programs to treat soil-transmitted helminths (*Ascaris lumbricoides*, hookworms, *Trichuris trichiura*) as per World Health Organization guidelines
Manufactures name	GlaxoSmithKline
Approval conditions	In Australia, albendazole is licensed for use but contra-indicated in pregnant women and those under the age of 2. In Vietnam, albendazole is licensed for use in those over the age of 1 year, including pregnant women after the first trimester, in accordance with World Health Organization guidelines.
Provision of product	Albendazole will be purchased from a local supplier in Vietnam.
Administration of product	Albendazole will be administered as a single dose of 400mg, as per World Health Organization guidelines.
Risks	Side effects of albendazole are generally mild, transient and self-limiting, and include epigastric pain, headache, nausea, and dizziness.

Investigational product dispensing and packaging

As this is not a blinded trial, albendazole will be packaged and labelled in normal packaging as received from the supplier. Albendazole will be distributed by research team staff to primary school-aged children at school (in line with the existing government-led biannual deworming program) in both study arms. In the intervention arm, albendazole will additionally be dispensed to all community members aged over 1 year, excluding pregnant women in the first trimester. This will be done house-by-house by research team staff. All medication will be taken under direct observation of research team staff.

Investigational product administration

As per World Health Organization guidelines, albendazole 400mg will be distributed as a single dose every six months. Albendazole 200mg will be administered to children aged under 2 years.

Trial Duration

The duration of the trial is 12 months. This will include a baseline visit at the beginning of the trial (November 2018), and two follow-up visits at six-monthly intervals (May 2019, November 2019).

Selection and Withdrawal

Recruitment

Primary schools will be selected at random (using a random number generator) for participation in the study, from a list of all primary schools in Dak Lak province that are in rural/remote locations and have between 200 and 500 students. After the schools have been selected, the process will then be as follows:

1. Initial meetings will be held between the research team and the school and hamlet leaders and local medical staff, to explain the aims and design of the study (The "Study explanation document" will be used as a guide and provided as written information). Verbal consent will be obtained to conduct the research in their school and hamlets. In the unlikely case of refusal, we will randomly select a replacement school from a pre-generated randomly selected list of replacement schools). Written informed consent will be obtained at this time from school headmasters for permission to answer a questionnaire regarding their school.
2. At this initial meeting, study participants will be selected from each school by selecting all children who reside in the 2 or 3 hamlets that send the most children to the school, to achieve a sample size as close to 150-180 as is feasible.
3. At study baseline, the school headmaster will request that parents and guardians of the children who have been selected to participate in data collection attend a meeting at the primary school. This will be done via an invitation letter sent to all parents along with a schematic study information sheet. At the parent meeting, the research team will explain the study in further detail, provide written information statements, and obtain written informed consent for sample collection and questionnaire completion (further details in section 8 below).
4. Once written information consent has been obtained from parents/guardians, the study will be explained to selected children (for whom consent was obtained) and they will be invited to participate in data collection.

In the intervention clusters, hamlet-level meetings will be arranged, to explain the study to all community members in the communities that will be receiving the deworming intervention. Written informed consent will be sought during house-to-house visits for albendazole distribution.

Eligibility Criteria

Eligible participants will be school-aged children attending the primary schools participating in the study, who are in grades 1-4 at baseline (aged 6-10 years). There are no specific exclusion criteria – all children who are in grades 1-4 whose parents provide informed consent will be eligible for participation in the study.

Withdrawal of study participants

All children in Dak Lak province already receive deworming medication twice per year at school, and the trial will be continuing this regular treatment. In the extremely unlikely event that a child reports a serious adverse event following

albendazole administration, he/she will not be given further doses of albendazole, but could continue participating in data collection.

If any children (or their parents/guardians), or other community members, do not wish to receive the treatment, they can refuse treatment. This will not be considered as them withdrawing from the trial. This is because the trial is designed to evaluate the impact of school- and community-wide deworming program, rather than the efficacy of medication on each individual. It is expected that coverage of children and community members will be less than 100%.

Children who are participating in the study – and their parents/guardians – may choose to withdraw from data collection at any time, and request that the data collected from them previously (stool samples and questionnaires) be removed. In this case, participants would not be replaced.

Study treatments and procedures

Data collection

Once written information consent has been obtained from parents/guardians, the study will be explained to selected children (for whom consent was obtained) and they will be invited to participate in data collection. Children and their parent/guardian will answer a questionnaire, administered as an interview by trained fieldworkers. The questionnaires will take approximately 10 minutes to complete and will relate to participants' access to water and sanitation, hygiene practices, home environment and socioeconomic status. Once questionnaires have been completed, children will be instructed as to how to collect a stool sample and provided with the materials to do so. They will be asked to collect an early morning stool sample the following morning and bring it with them to school, where the sample will be delivered directly to the research team. The research team will process the stool sample immediately in the field by preparing two aliquots of stool: one with no preservative for analysis using microscopy at Tay Nguyen University, and one preserved in 5% potassium dichromate for analysis using quantitative PCR at the University of Melbourne, Australia.

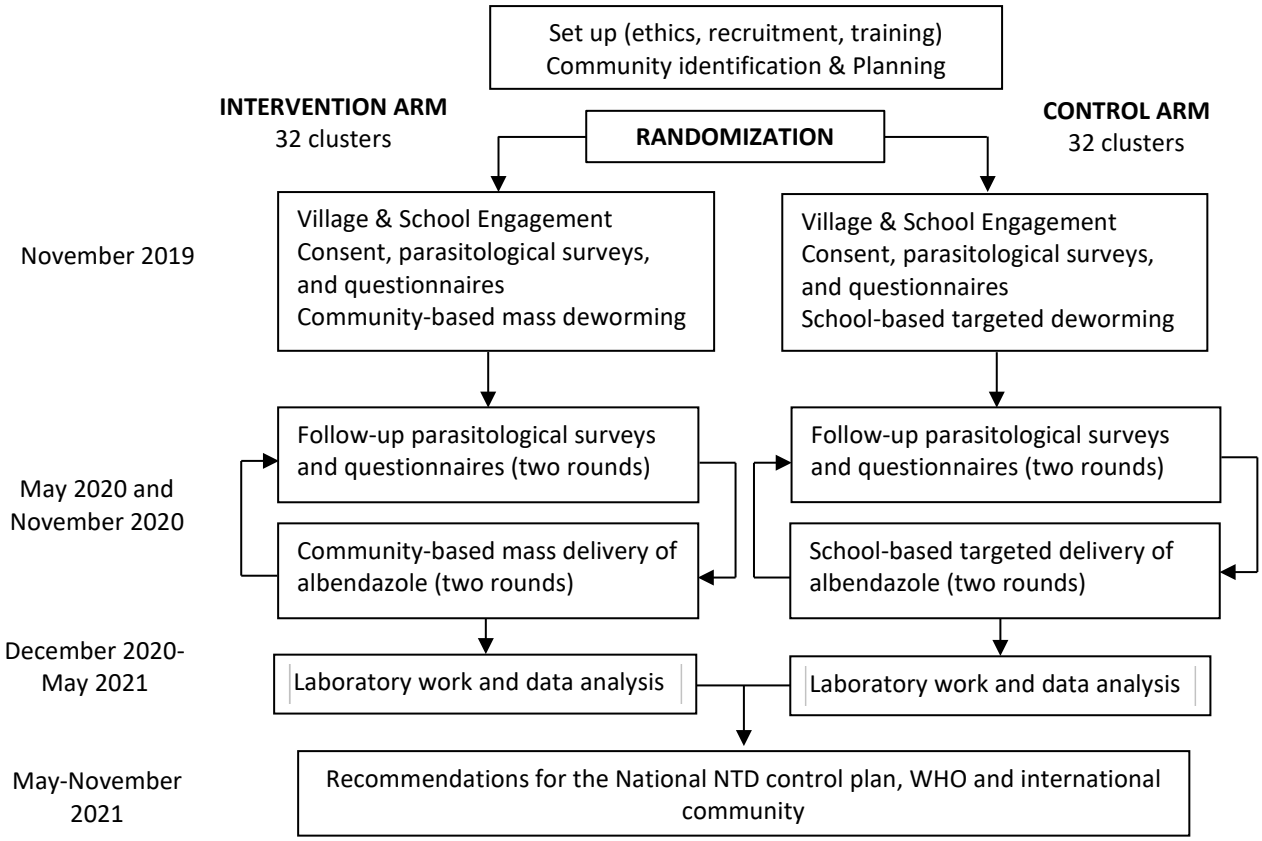
Two further rounds of data collection will be conducted at six-monthly intervals. At these follow-up time points, stool samples will be collected using the same procedures described above. Questionnaires will not be completed.

Study intervention

In both study arms, school-based targeted deworming will be delivered. This will involve distributing albendazole (400mg orally) to the children attending the primary school (grades 1-5, typically aged 6-11 years). Distribution will occur every at baseline and at two six-monthly follow-up visits, at the same time as the government standard school-based deworming program.

In the intervention arm of the study, community-based mass deworming will additionally be delivered. This will involve distributing albendazole (400mg orally) to all community members (aged over 1 year, excluding pregnant women in the first trimester) using a community-based delivery system. Children under 2 years will take half a dose (200mg) as per WHO guidelines. Distribution will occur every at baseline and at two six-monthly follow-up visits.

Study Flow Chart



Contraindications

There are no contraindications to participation in data collection. In the extremely unlikely event that a child reports a serious adverse event following albendazole administration, he/she will not be given further doses of albendazole, but could continue participating in data collection.

Subject compliance

All doses of albendazole will be provided to participants directly by members of the research team and taken under direct observation. Where household members are absent at the time of the research team's visit, doses of albendazole will not be left in the household for absent members to take later. A return visit from the research team to the household will be arranged where possible (either later the same day or the following day), to treat the absent household members.

Safety Monitoring and Reporting

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment. **Reporting** • A record of all adverse event reports will be recorded by the research team.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered. **Reporting** • A record of all adverse event reports will be recorded by the research team.

Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)	Any adverse event/adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. **Reporting** • Any serious adverse events will be reported via email to humanethics@unsw.edu.au using the UNSW safety monitoring report form • These will also be reported to the HREC at Tay Nguyen University
Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. **Reporting** • Reports defined as an **urgent safety measure** that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial will be reported via email to humanethics@unsw.edu.au using the UNSW safety monitoring report form **within 72 hours.** • Reports defined as significant safety issues should be notified via email to humanethics@unsw.edu.au using the UNSW safety monitoring report form **within 15 calendar days** of the research team becoming aware of the issue. • These will also be reported to the HREC at Tay Nguyen University
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Definition: An adverse reaction that is both serious and unexpected. **Reporting** • All **suspected unexpected serious adverse reactions** occurring in Australian participants will be reported to the Vietnam Ministry of Health and the HREC at UNSW and Tay Nguyen University within 15 calendar days of becoming aware of the case. • All fatal or life threatening Australian **suspected unexpected serious adverse reactions** will be reported to the Vietnam Ministry of Health and the HREC at UNSW and Tay Nguyen University via email to humanethics@unsw.edu.au using the UNSW safety monitoring report form immediately, but no later than **7 calendar days** after being made aware of the case, with any follow-up information within a further 8 calendar days.

Sample size and statistics

The sample size calculation was performed as follows:

We used the generalized linear model described in our recent meta-analysis of STH reinfection after deworming, that predicts the impact of mass vs targeted treatment on prevalence reduction in school-aged children, adjusted for baseline prevalence, number of doses and follow-up time [11]. For hookworm, assuming a baseline prevalence of 20% (based on our preliminary surveys conducted in Dak Lak in December 2018), the model predicts a prevalence reduction of 85% after mass deworming vs 56% in the targeted approach, after 2 rounds of deworming and 6 months follow-up. Assuming an average cluster size of 120 and an intra-cluster correlation of 0.12, with a power of 80% and α=0.05, the required sample size is 32 elementary schools in each arm, which will be randomised 1:1 between the two arms. The ICC was estimated based on the WASH for WORMS trial in Timor-Leste [16].

Therefore, the study will take place in 64 primary schools – 32 in each arm. Given sample size requirements and budget constraints, the study will take place in schools that have between 200 and 500 children enrolled. To achieve the required sample size of 120 children per cluster, we will aim to enrol up to 180 children per school at baseline, allowing for 20% of children to not provide an initial stool sample and 15% loss to follow-up during the study period.

The primary outcome is the prevalence of hookworm (unspeciated) measured at the final follow-up. Secondary outcomes are prevalence of *N. americanus*, *Ancylostoma duodenale*, and *Ancylostoma ceylanicum* (i.e. species-specific hookworm infections), and prevalence of *A. lumbricoides* and *T. trichiura*, measured at the final follow-up. Additional secondary outcomes are the mean intensity of infection (calculated as the average number of eggs per gram of faeces, derived from the Ct values obtained using quantitative PCR) of each STH, measured at the final follow-up. Each of the trial outcomes will be compared between control and intervention arms.

Generalized linear mixed models will be used to account for within and between cluster variability. If there is a need to adjust for confounding or differences in the baseline characteristics of the intervention and control groups, variables measured in the study questionnaires will be incorporated as covariates, allowing an adjusted effect estimate to be calculated for the intervention. For prevalence, Bernoulli logistic regression models will be developed with the infection status of the individual as the outcome, and for infection intensity, linear regression models will be developed. For all models, age and sex will entered as covariates, and school as a random effect. Adjustment for baseline prevalence will involve entering baseline prevalence as fixed effect. The intervention will be entered as a binary fixed effect to estimate differences in prevalence and intensity, and a relative risk of infection, comparing the two arms at each follow-up survey. All analyses will be conducted using Stata software, and a 5% level of significance will be used.

Ethics

HREC Name	**Ethics Reference**	**Ethics approval date**	**Ethics expiration date**
HREC University of New South Wales	HC190136	7th May 2019	6th May 2024
HREC Tay Nguyen University, Vietnam	1804-QD-DHTN-TCCB	18th March 2019	1st September 2021