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[Intervention Protocol]

Short versus long drug regimens for Chagas disease

Samanta Díaz Menai¹, Lucia B Varela¹, Camila Micaela Escobar Liquitay¹, Marilina Santero^{2,3}, Javier Bracchiglione^{2,4,5}, Luis Garegnani¹

¹Cochrane Associate Centre, Universidad Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. ²Iberoamerican Cochrane Centre, Institut de Recerca Sant Pau (IR Sant Pau), Barcelona, Spain. ³Universitat Autònoma Barcelona, Barcelona, Spain. ⁴Interdisciplinary Centre for Health Studies CIESAL, Universidad de Valparaíso, Viña del Mar, Chile. ⁵CIBER de Epidemiología y Salud Pública, Instituto de Salud Carlos III, Madrid, Spain

Contact: Samanta Díaz Menai, samantadiazmenai@gmail.com.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of short versus long drug regimens (trypanocidal schemes) for Chagas disease in chronic asymptomatic stages.

BACKGROUND

Description of the condition

Chagas disease, caused by the parasite *Trypanosoma cruzi*, remains a significant public health challenge, with more than seven million people infected globally, primarily in Latin America, where the disease is endemic in 21 continental countries. Despite its growing global presence, transmission is still largely linked to vector exposure in these regions. The most recent incidence data from 2024, reported by the World Health Organization (WHO) and Pan American Health Organization (PAHO), estimate 30,000 to 40,000 new cases annually [1]. Each year, Chagas disease results in approximately 10,000 to 12,000 deaths worldwide, and more than 100 million people are currently at risk of infection [1].

Vector-borne transmission has been reduced through international strategies, notably triatomine bug control. However, changes in population migratory dynamics, along with parenteral (transfusional, solid organ donation) and vertical transmission, have expanded the disease beyond endemic regions, making it a global problem [2, 3].

After the ‘acute-phase’, which is usually asymptomatic, parasitemia levels fall below detectable thresholds for microscopes. This stage is followed by a ‘chronic phase’, which can last for a lifetime. Most of these people will never develop clinically apparent disease, presenting what is known as ‘indeterminate chronic phase’ [4], characterized by a normal 12-lead electrocardiogram (ECG), normal chest radiographs, and normal imaging of the esophagus and colon [5]. In this phase, *T. cruzi* lodges in organ tissue, inducing a specific immune response with high titers of anti-*T. cruzi* antibodies, and may remain asymptomatic for 30 to 40 years [6]. Approximately 30% of people with the chronic form will subsequently develop a stage determined by visceral affection. This advanced phase is known as the ‘chronic symptomatic phase’ of the disease. The most common and severe clinical manifestation is Chagas cardiomyopathy, which can range from ECG abnormalities without clinical correlation to dilated cardiomyopathy accompanied by ventricular fibrillation, heart failure, thromboembolic events, arrhythmias, and sudden death [5]. Gastrointestinal involvement occurs in 15% to 20% of patients and is more prevalent in endemic areas, according to prevalence studies [7]. The esophagus and colon are the most affected organs. Changes in nervous tissue lead to motility disorders, ultimately resulting in organ dilation, referred to as megacolon and megaesophagus [8, 9].

Description of the intervention and how it might work

Currently, only two drugs have proven efficacy against *T. cruzi*: benznidazole (BZN) and nifurtimox (NFX). Benznidazole is a nitroimidazole derivative introduced for human treatment in 1971. Since then, various clinical and experimental studies have confirmed its effectiveness for both acute and chronic Chagas disease, establishing BZN as the first-line treatment for both conditions [10, 11]. Benznidazole acts as a prodrug, activated by the trypanosomal enzyme nitroreductase, which releases reactive molecules such as dialdehyde glyoxal. These molecules make the parasite vulnerable to oxidative damage at all stages of its life cycle. The drug works through complex mechanisms, affecting protein, RNA, and DNA synthesis while promoting parasite clearance in infected hosts [12]. Benznidazole is primarily absorbed via the gastrointestinal tract, with renal elimination as the predominant

excretion pathway, although about 20% is excreted in the feces. It has oral bioavailability of over 90%.

Nifurtimox is a nitrofuran derivative first used clinically in 1969. Studies have shown varying efficacy based on factors such as disease stage, treatment duration, patient age, and geographic region. Nifurtimox produces nitroanion radicals through the action of nitroreductases, and in the presence of oxygen, these radicals generate free radicals that damage *T. cruzi*. Like benznidazole, nifurtimox inhibits DNA synthesis and accelerates its degradation. It is effective against the amastigote, epimastigote, and reproductive forms of the parasite. NFX is absorbed through the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver, involving cytochrome P-450 and P-450 reductase. Renal excretion is minimal (less than 1%). Due to its higher toxicity, nifurtimox was discontinued, and its commercialization was halted in Brazil, Argentina, Chile, and Uruguay in the early 1980s. However, due to the lack of alternatives, it remains a second-line treatment option when benznidazole fails or causes significant toxicity [13].

The efficacy of available drug schemes' length of treatment remains questionable, mainly during the chronic stage of the disease. Prolonged regimens are required, which favors the occurrence of drug-related adverse events [14]. It was once thought that the chronic symptoms of Chagas disease were mainly caused by an overactive immune response, making antiparasitic treatment ineffective for adults in the chronic phase. However, long-term studies in Latin America have shown improved clinical outcomes in adults treated with benznidazole or nifurtimox, supporting the current understanding that the persistence of the parasite plays a significant role in the disease's pathology [15, 16].

Given the current body of evidence, foregoing treatment at this stage is not a viable option. Recent studies have demonstrated that chronically ill people treated with benznidazole exhibit a significant reduction in blood antibodies compared to those receiving a placebo. On the other hand, the BENEFIT trial, a multinational randomized study comparing benznidazole and placebo in people with advanced Chagas cardiomyopathy (CCM), did not find a significant difference in outcomes between the two groups. This underscores the importance of initiating antiparasitic treatment as early as possible in acute or indeterminate patients, prior to the onset of more severe forms of CCM [17]. Furthermore, there is evidence suggesting that, even in the absence of a complete cure, the treatment group experienced fewer electrocardiographic abnormalities. This finding may be attributed to the delay in tissue damage [18, 19, 20, 21].

Whether to treat Chagas disease in asymptomatic chronic stages is still a difficult point to elucidate based on the available evidence. A guideline from PAHO suggests offering trypanocidal treatment to people with chronic *T. cruzi* infection and no specific organ damage, although this recommendation is based on low-certainty evidence for the effects of this intervention, according to the GRADE approach [22, 23]. In this context, there is an urgent need for more effective and safer trypanocidal schemes, particularly during the chronic stage.

Why it is important to do this review

Thirty-day schemes have been used in non-randomized intervention studies, suggesting they might be as effective as longer regimens and may prevent severe effects like peripheral

neuropathy and bone marrow depression [16]. However, 30-day schemes may not prevent the most frequent adverse events like dermatitis and digestive intolerance. This raises the question of whether shorter regimens could reduce major side effects and improve patient compliance compared to the standard 60-day schemes. The current recommendations suggest that 30 days of treatment could be considered a complete course, although the evidence regarding the duration of these regimens remains uncertain [24].

The rationale for this Cochrane review lies not only in the fact that shorter treatment duration would facilitate better adherence for patients and improve accessibility and availability of treatment, but also in its potential to improve efficiency in resource allocation. Providing a comprehensive and updated synthesis of evidence, this review is expected not only to guide informed decisions but also to identify critical areas for future research needs. Addressing uncertainties guides policymaking for more targeted and impactful strategies. Regarding the degree of uncertainty, the current evidence base surrounding Chagas disease treatment contains uncertainties, possibly due to variations in study findings, conflicting data, or limitations in available research. We consider that the importance for patients relies on understanding the most effective treatment options, the direct impact that shorter treatment schemes could have on health outcomes, e.g. in reducing treatment withdrawal due to adverse events and, consequently, improving adherence to it, quality of life, and potential recovery from this condition. For health professionals, it would help in decision-making about treatment. For policymakers, it would help to shape public health policies regarding the allocation of resources through a more efficient use of them.

OBJECTIVES

To assess the effects of short versus long drug regimens (trypanocidal schemes) for Chagas disease in chronic asymptomatic stages.

METHODS

We will follow the Methodological Expectations for Cochrane Intervention Reviews when conducting the review [25], and PRISMA 2020 for the reporting [26].

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) and cluster-randomized controlled trials (cluster-RCTs). Following the guidelines in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [27], we will exclude cross-over trials due to potential carry-over effects after the wash-out period.

We will include studies published as full text, as well as those available as abstracts only and unpublished reports if they provide enough information to determine their eligibility.

Types of participants

We will include RCTs involving adults (≥ 18 years) of any gender diagnosed with Chagas disease in its chronic asymptomatic stage, which is characterized by persistent infection without apparent symptoms. Diagnoses must be confirmed through positive serology

using at least two of the following techniques: enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination (IHA) or indirect immunofluorescence (IIF), or as defined by the studies' authors. Participants will be included regardless of their baseline ECG results, as cardiac conduction abnormalities are often asymptomatic. We will also include individuals regardless of immune status, such as those with hematological malignancies, cancer, transplants, hypogammaglobulinemia, or HIV. For studies where the clinical status of the infected population is not clearly defined, we will interpret this based on the population description (e.g. outpatients not receiving supportive treatment) or seek clarification from the authors. Our aim is to include studies in which at least 80% of the participants are asymptomatic.

We will exclude RCTs involving people with signs or symptoms of chronic cardiac or digestive forms of Chagas disease. Additionally, we will also exclude RCTs involving pregnant or breastfeeding women because treatment with available tripanocydals is contraindicated during pregnancy due to limited safety evidence. While some guidelines advise against their use during breastfeeding [28], others do not share this restriction [24], as some research indicates absorption of this drug through breastmilk does not pose a risk to infants [29]. Nonetheless, due to these conflicting recommendations, we will exclude studies involving this population.

Types of interventions

We will include RCTs examining short drug regimens (SDR) as the intervention, defined as treatments lasting less than four weeks [23, 24], or as specified by the study authors. We will include RCTs examining long drug regimens (LDR) as comparators, defined as treatments lasting longer than four weeks [28], or as specified by the study authors.

We will consider drug regimens as any oral treatment offered to study participants with a confirmed diagnosis of Chagas disease, intended for clearance or reduction of mean antibody titers to *T. cruzi*, as stated by the authors. We will include studies administering different trypanocidal drugs, including nitroimidazolic derivatives, such as nifurtimox (NFX) and benznidazole (BZN) or non-nitroimidazolic derivatives, such as allopurinol (ALLOP), itraconazole (ITRA) and other drugs meeting the criteria for our definition of regimens.

We will compare drug regimens (short vs long) regardless of the drug used, as long as it involves a trypanocidal scheme.

We will exclude RCTs involving combination therapies where the trypanocidal component extends beyond the defined short duration or those without clear definitions or criteria for what constitutes a short regimen.

Outcome measures

We will consider the following outcomes in this review.

Critical

1. Incident chagasic cardiac disease.
2. Incident chagasic gastrointestinal affectionation.
3. Adverse events related to pharmacological interventions.

Important

1. Mortality.
2. Hospitalization due to Chagas disease complications or related conditions.
3. Treatment adherence.
4. Sustained parasitological clearance.

We will not exclude RCTs if they fail to report more than one of our critical or important outcomes. However, we will exclude RCTs if none of our outcomes of interest were measured, provided there is evidence to support this, such as contact with trial authors or access to the original protocol.

Critical outcomes

1. Incident chagasic cardiac disease: defined as the emergence of changes in diagnostic tests or clinical status necessitating hospitalization, the implantation of cardiac devices, or resulting in death. For participants with a normal ECG at baseline, incident disease will be defined as the development of two new ECG abnormalities or a single ECG abnormality typically requiring medical intervention (e.g. ventricular tachycardia, atrial fibrillation or flutter, complete A-V block), or as defined by study authors. In studies utilizing Kuschner's classification criteria [30], incident disease will be considered as a change of at least two stages during the follow-up period. Specifically, this includes infected individuals with a normal ECG at baseline (stage 0) who developed cardiomegaly (documented through any imaging method) or symptoms of heart failure (stage II).
2. Incident chagasic gastrointestinal affectation: referring to the occurrence of damage or dysfunction in the gastrointestinal tract, or as defined by the authors. These changes may involve dysphagia, esophageal pain, regurgitation, pyrosis, hiccups, cough, parotid hypertrophy, and weight loss. At the colon level, non-ectasic colonopathy is demonstrated by manometry and by the response to methacholine, as symptoms, such as obstipation arises only when the megacolon becomes installed [31].
3. Adverse events related to pharmacological interventions: assessed as the frequency of mild to moderate events (e.g. headache, nausea, dyspepsia, pruritus) or severe events requiring discontinuation of therapy or hospitalization, as described by the authors. We will include any symptom potentially associated with the treatment that the authors recorded in the treated groups and categorized as either mild-to-moderate (e.g. headache, nausea, dyspepsia, pruritus) or severe. Severe outcomes may include conditions that, according to the authors, necessitated discontinuation of therapy or hospitalization (e.g. seizures, fever, Stevens-Johnson syndrome, severe dermatitis, leukopenia, or toxic hepatitis).

The anticipated timeframe for the development of clinical endpoints in Chagas disease varies depending on the manifestation. For incident chagasic cardiac disease, progression typically occurs over years or decades, with the indeterminate chronic phase lasting 10 to 20 years in most people before advancing to cardiac complications such as Chagas cardiomyopathy. For gastrointestinal affectation, progression also tends to occur over many years, though specific timelines are less well-defined. These extended timeframes highlight the importance of ensuring adequate follow-up duration in included studies to

capture these outcomes and interpret findings effectively [32]. We will include studies with a minimum duration of follow-up of 12 months.

Important outcomes

1. Mortality: assessed as a dichotomous outcome for Chagas disease-specific deaths. Additionally, the frequency of all-cause mortality following diagnosis will be extracted and reported separately as a dichotomous outcome, when available.
2. Hospitalization due to Chagas disease complications or related conditions: defined as any condition potentially related to Chagas disease that authors decided to record in the treated groups.
3. Treatment adherence: assessed as a continuous outcome when measured with the Medication Adherence Report Scale-5 (MARS-5) scale [33] or the 8-item Morisky Medication Adherence Scale (MMAS-8) [34], or any other reported by the authors at the end of treatment. We will also assess treatment adherence as a dichotomous outcome, defined as the frequency of suspension or discontinuation of medication intake.
4. Sustained parasitological clearance: defined as persistent negative polymerase chain reaction (PCR) results from the end of treatment until a specified time point defined by the authors or at the end of follow-up. We will also consider as parasitological clearance the negativization of serological tests, defined as clearance or reduction of mean antibody titers to *T. cruzi* after end of treatment compared to pretreatment results, demonstrated by any of the following: hemagglutination, indirect immunofluorescence, or ELISA.

Search methods for identification of studies

Electronic searches

We will search the following databases from the inception of each database to the date of the search; we will place no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (from inception to date of search)
- MEDLINE (Ovid MEDLINE ALL; 1946 to date of search)
- Embase (Ovid; 1974 to date of search)
- Latin American and Caribbean Literature in Health Sciences (LILACS: from inception to date of search)

We will search the following trial registries.

- WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch)
- ClinicalTrials.gov (www.clinicaltrials.gov; from inception)

The details of the search strategies can be found in [Supplementary material 1](#).

Searching other resources

We will search for gray literature in the following resources.

- CEPAL/ Social Development Network of Latin America and the Caribbean (dds.cepal.org/)
- Chagas Clinical Research Platform (dndi.org/global-networks/chagas-platform/)

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- ISGlobal: Barcelona Institute for Global Health (www.isglobal.org/en/home)
- La Referencia (www.lareferencia.info/es/)
- MedRxiv (www.medrxiv.org/)
- Open Grey (opengrey.eu/)
- Pan American Health Organization (PAHO) (www.paho.org)
- ProQuest; dissertation and theses

Before publication, we will verify all included studies that contain any amendments, comments, or retractions.

Data collection and analysis

Selection of studies

We will utilize Covidence software for the selection of studies [35]. Two review authors (SDM, LBV) will independently screen the titles and abstracts of all records retrieved from the searches. Any disagreements will be resolved through consensus or by consulting a third review author (LG, MS, or JB). We will obtain the full texts of all potentially relevant records for further evaluation. Any disagreements will be resolved through consensus or by consulting a third review author (LG, MS, or JB). If consensus cannot be reached, we will categorize the study as ‘awaiting classification’ and contact the study authors for clarification. We will present a PRISMA flow diagram to illustrate the study selection process [26]. Additionally, we will compile a table listing all articles excluded after full-text assessment along with the reasons for their exclusion.

Data extraction and management

For studies meeting our inclusion criteria, two reviewers (SDM and LBV) will independently extract essential information about participants, interventions, and comparators using a standard data extraction template, which we will pilot test beforehand. Any disagreements between reviewers will be resolved through discussion with a third reviewer (LG) consulted if necessary.

One reviewer (SDM) will enter data into Review Manager (RevMan) [36]. Two other reviewers (LG, LBV) will verify and transfer study data into the analyses.

We will extract several key data points from the reports. These include study methods, such as design, dates (start and end or, if unavailable, noted as missing), settings, country, language of publication, and study identifier. For participants, we will gather inclusion and exclusion criteria, participant details, baseline demographics (including mean age, age range, gender, Chagas disease diagnostic criteria, baseline ECG, place of residence, race/ethnicity/culture/ language and occupation), and the number of participants in each treatment group with outcome events. Interventions and comparisons will follow the Template for Intervention Description and Replication (TIDieR) checklist, detailing the intervention’s name, rationale, materials, procedures, provider expertise, delivery mode, location, frequency, tailoring, modifications, and adherence measurements [37]. For outcomes, we will identify relevant outcome definitions, measurement methods, timing, and any specific subgroups relevant to the review. Additionally, we will document the study funding sources and any declarations of interest by primary investigators.

We will report these data in the characteristics of the included studies table and summarize them in Table 1.

We will contact the authors of the included studies to clarify questions about their studies and document all communications. If additional information is needed, we will reach out to the primary authors.

In cases of duplicate publications, companion documents, or multiple reports of a primary study, we will combine all available data to use the most complete dataset across publications. Duplicate publications, companion documents, and trial documents will be listed as secondary references under the relevant study ID. This applies to both included and excluded studies.

If data from included studies are available in clinical trial registers, such as ClinicalTrials.gov, we will fully utilize this information. If discrepancies are found between published and registry data, we will seek clarification from study authors; unresolved discrepancies will be noted in the review report. Studies labeled as ‘completed’ in trial registers without further information (study results, publication, or both) will be added to the studies awaiting classification.

Risk of bias assessment in included studies

In this risk of bias assessment plan, two authors (SDM and LBV) will independently evaluate the risk of bias in outcomes included in the summary of findings table (see [Certainty of the evidence assessment](#)) using the Cochrane RoB 2 tool [38, 39]. We will resolve disagreements through consensus or consultation with a third author (LG). When relevant data are missing from publications, trial protocols, or clinical study reports, we will contact study authors for additional information on risk of bias items.

The assessment will cover the following domains, focusing on the initial effect of assignment to interventions: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported results [40].

We will use the answers to the signaling questions and supporting information to make a collective domain-level judgment of low risk, some concerns, or high risk of bias. An overall risk of bias for each outcome will be assigned based on these domain-level judgments. The criteria are as follows.

- Low risk: all domains judged as low risk.
- Some concerns: one or more domains judged to have some concerns.
- High risk: one or more domains judged as high risk, or if there are some concerns in four domains.

Each judgment will include a direct quote and justification from the study report, recorded in the risk of bias table. We will then summarize the overall risk of bias judgments across studies and domains.

When evaluating biases related to deviations from intended interventions, the assessment will focus on the effect of assignment to intervention [38]. We will also review trial registries, protocols, and analysis plans to assess selective reporting. If risk of bias information includes unpublished data or trialist correspondence, we will note this in the table. In assessing treatment effects, we will evaluate the risk of bias for studies that contribute to that outcome. Summary assessments of risk of bias will be

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developed for each important outcome, across relevant domains, both within individual studies and across all studies [40]. We will use the RoB 2 Excel tool to manage data supporting the answers to signaling questions and risk of bias judgments (available at www.riskofbias.info/). All related data will be publicly accessible as supplementary material in a public repository.

For cluster-RCTs, we will apply additional considerations following the archived version of the RoB 2 tool for cluster-RCTs, domain 1b: bias arising from the timing of identification and recruitment of participants; available at www.riskofbias.info/, as outlined in the *Cochrane Handbook*, Section 23.1.2 and Table 23.1.a [27].

Measures of treatment effect

We will present dichotomous data (e.g. participants with adverse events) as a risk ratio (RR) with 95% confidence intervals (CIs). For continuous outcomes (e.g. treatment adherence), we will estimate the intervention effect using the mean difference (MD) with 95% CIs. In cases where studies utilize different instruments to measure the same outcome, we will calculate standardized mean differences (SMDs) with 95% CIs. We will enter data presented as a scale with a consistent direction of effect, and multiply the SMD by a standard deviation (SD) representative of the pooled studies, such as the SD from a well-established scale used across several studies included in the analysis. We will only conduct a meta-analysis when it is appropriate, meaning that the treatments, participants, and underlying clinical questions are sufficiently similar to justify pooling the data. Additionally, we will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

We will consider the level at which randomization occurs and account for multiple observations of the same outcome. If more than one comparison from the same study is eligible for inclusion in a single meta-analysis, we will either combine groups to create a single pairwise comparison or appropriately reduce the sample size to ensure that the same participants do not contribute data more than once (by splitting the shared group into two or more groups). While the latter approach helps adjust the precision of the comparison, it does not address the correlation that arises from including the same participants in multiple comparisons [40].

The unit of analysis will be participants with chronic Chagas disease. For cluster-RCTs, we will consider the cluster as the unit of analysis rather than individual participants, to avoid unit of analysis errors as outlined in Section 23.1.1 of the *Cochrane Handbook* [27]. If the effect measure for the cluster is not determined using appropriate methods in the included studies, we will adjust the standard error of the effect estimate (from an analysis that ignores clustering) by multiplying it by the square root of the design effect, calculated using an intraclass (or intraclass) correlation coefficient (ICC) of 0.02, following guidance in Sections 23.1.4 and 23.1.5 of the *Cochrane Handbook*. [27].

Dealing with missing data

When possible, we will obtain missing data from the authors of the included studies. Important numerical data, such as the number of participants screened, randomly assigned, and analyzed in intention-to-treat, as-treated, and per-protocol populations, will be carefully evaluated in our risk of bias assessments. We will review attrition rates, including dropouts, losses to follow-up, and

withdrawals, and critically examine issues related to missing data and imputation methods, such as last observation carried forward. We will analyze available data only. When this is not feasible and missing data are likely to introduce significant bias, we will assess the impact of including these studies through a sensitivity analysis.

Reporting bias assessment

To limit reporting bias, we will conduct an extensive literature search without restrictions on publication date or language. We will examine study protocols and trial registrations to assess selective reporting. For comparisons and outcomes with 10 or more studies included, we will use funnel plots to assess small-study effects. Possible explanations for funnel plot asymmetry include true effect heterogeneity based on study size, methodological flaws leading to small-study bias, and selective non-reporting [41]. We will interpret these results carefully [42].

Synthesis methods

We will complete all syntheses in RevMan [36]. We plan to conduct a meta-analysis only if we determine that participants, interventions, comparisons, and outcomes are sufficiently similar to produce clinically meaningful results. Our primary approach will be to summarize data using a random-effects model [43], interpreting these analyses with consideration of the entire distribution of effects and presenting a confidence interval. Statistical analyses will follow the guidelines outlined in the *Cochrane Handbook* [44], and we will conduct subgroup analyses using the methodology recommended by Deeks and colleagues, as described in Section 10.11.3 of the *Cochrane Handbook* [44].

Investigation of heterogeneity and subgroup analysis

We will visually examine the variability in point estimates and the overlap in confidence intervals. To estimate the degree of heterogeneity among trials in each analysis, we will calculate the I^2 statistic [45]. When we detect substantial unexplained heterogeneity, we will report it and investigate possible causes through prespecified subgroup analysis. If we encounter significant clinical or methodological heterogeneity, we will not report study results as a pooled effect estimate in a meta-analysis.

We will use this rough guide to interpretation, outlined in Chapter 10 of the *Cochrane Handbook* [44].

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

We will avoid using absolute cutoff values, instead interpreting I^2 in relation to (a) the size and direction of effects and (b) the strength of evidence for heterogeneity, such as the P value from the χ^2 test or the confidence interval for I^2 . We anticipate that certain characteristics will introduce clinical heterogeneity, so we plan to conduct subgroup analyses for these factors and investigate any interactions [46] based on the following.

- Nitroimidazole derivatives (e.g. nifurtimox [NFX] and benznidazole [BZD]) or non-nitroimidazole derivatives (e.g. allopurinol, itraconazole), along with other drugs that meet the criteria for our definition of regimens.

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- Male versus female, considering trials conducted on one gender exclusively or with over 80% of participants representing a specific gender to establish the subgroups.
- Normal ECG versus abnormal ECG at baseline.
- Place of residence: considering people living in rural, semi-rural, and urban areas.
- Race/ethnicity/culture/language: indigenous populations (e.g. Quechua, Aymara, Mapuche, Guarani, Wayuu, etc.) or non-indigenous.
- Occupation: categories according to the International Standard Classification of Occupations (ISCO-08) by the International Labour Organization [47].

We will apply the formal test for subgroup interactions in RevMan [36], recognizing its limitations because it relies on observational data and has limited power to detect differences when there are fewer than 10 studies per category [40].

Equity-related assessment

Chagas disease, endemic to Latin America, serves as a clear example of how social and economic inequalities impact access to healthcare and treatment opportunities. Health equity becomes a fundamental principle in addressing this issue, as living conditions, socio-economic status, occupation, and other determinants significantly influence the prevalence and management of this disease. We will address equity-related assessments by assessing the effects of the intervention in the following groups, from the PROGRESS-PLUS framework (see [Investigation of heterogeneity and subgroup analysis](#)).

- Place of residence: Chagas disease is predominantly found in rural and semi-rural areas, where inadequate infrastructure and poor housing conditions prevail. Communities in these regions frequently encounter limited access to healthcare services, creating significant barriers to the timely diagnosis and effective treatment of the disease [48, 49].
- Race/ethnicity/culture/language: indigenous populations are disproportionately affected by Chagas disease, facing cultural and linguistic barriers that limit their access to prevention and treatment information. Discrimination and stigma further worsen their situation. Approximately six to seven million people are infected with *T. cruzi* globally, with infection rates in some indigenous communities reaching as high as 35.4%, while less than 1% of those infected receive adequate medical treatment [50, 51].
- Occupation: individuals affected by Chagas disease often come from informal or agricultural labor sectors, which implies unsafe working conditions and a lack of social protection. This not only limits their economic capacity to seek medical attention but also perpetuates the cycle of poverty [52].
- Gender: women, particularly those of childbearing age, face additional risks due to the congenital transmission of the parasite. Furthermore, gender inequalities may limit their access to economic and educational resources, impacting their ability to seek medical care [53].

For the subgroup analysis, we will extract disaggregated data on place of residence, race/ethnicity/culture/language, occupation, and gender. If these data are not reported, we will contact the authors to obtain them.

We will create a standalone summary of findings table to present all results related to health inequities. Additionally, in the conclusion sections titled 'Equity-related Implications for Practice' and 'Equity-related Implications for Research', we will analyze how the findings pertain to the diverse populations included in our subgroups, highlighting potential disparities and context-specific factors that may influence outcomes and the applicability of practices. The equity-related characteristics of participants that inform the interpretation of results are detailed in [Supplementary material 2](#).

Sensitivity analysis

We plan to perform the following sensitivity analyses for the critical outcome.

- Excluding studies with cluster randomization.
- Removing studies with an overall high risk of bias.

Certainty of the evidence assessment

We will present a summary of the evidence in a summary of findings table, detailing the best estimate of the effect's magnitude, both in relative terms and absolute differences, for each relevant comparison of alternative management strategies. This table will include the number of participants and studies addressing each important outcome, along with a rating of overall confidence in the effect estimates for each outcome. We will use the methods outlined in the *Cochrane Handbook* [54], along with RevMan and GRADEpro GDT software, to create the summary of findings table [36, 55, 56]. If meta-analysis is not feasible, we will present the results narratively within the summary of findings table. Justifications for any decisions to downgrade the certainty of evidence will appear in informative footnotes, following GRADE guidelines for clear statements [55]. We will create a summary of findings table for the following comparisons and outcomes.

Comparisons

- Short versus long trypanocidal schemes

Outcomes

- Incident chagasic cardiac disease
- Incident gastrointestinal affection
- Adverse events related to pharmacological interventions
- Chagas-disease-specific mortality
- Hospitalization due to Chagas disease complications or related conditions
- Treatment adherence

Consumer involvement

Consumers will not be involved in this review.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: [10.1002/14651858.CD016172](https://doi.org/10.1002/14651858.CD016172).

Supplementary material 1 Search strategies

Supplementary material 2 Summary of the characteristics of participants we would expect to see in the evidence and the actual participant characteristics extracted from the included studies

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

Cochrane Editorial Service supported the authors in the development of this protocol.

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Martin Meremikwu, Professor of Paediatrics, University of Calabar, Calabar, Nigeria
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Colleen Ovelman, Cochrane
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- Peer-reviewers (provided comments and recommended an editorial decision): Sarah Louise Klingenberg, Cochrane Hepatobiliary Group (search review); Jennifer Hilgart, Cochrane (methods review)

Contributions of authors

All review authors read and approved the final protocol draft.

SDM, LBV, MS, JB, LG: conceptualization, protocol draft, searched studies for the [Background](#) section.

CE: [Search methods for identification of studies](#) development.

Declarations of interest

SDM: none known.

LV: none known.

MS: Marilina Santero is a consultant with the World Health Organization (Department of Non-Communicable Diseases, Disability and Rehabilitation). She is not involved in developing policies or primary research related to the topic of this review. She is an international technical expert working on the Global Status Report on Cancer 2025.

JB: none known.

LG: none known.

CE: none known.

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Registration and protocol

This is the protocol of the review.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analyzed.

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ADDITIONAL TABLES

Table 1. Table 1: Overview of included studies and synthesis table

Study	Study design	Population (sample size: intervention/control)	Type of intervention	Comparator	Outcomes with available data (synthesis method/metric)	Outcome timepoint	Synthesis methods
Author / year							