A community based study to compare the safety, efficacy and acceptability of a triple drug regimen (Ivermectin, Diethylcarbamazine and Albendazole) with a two-drug regimen (Diethylcarbamazine and Albendazole) for lymphatic filariasis elimination programme

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Delhi and Karnataka

Duration of the study
July 2016 – March 2018

Funding agency

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(Revised on 20 September 2017 for Phase II study – effectiveness and efficacy)

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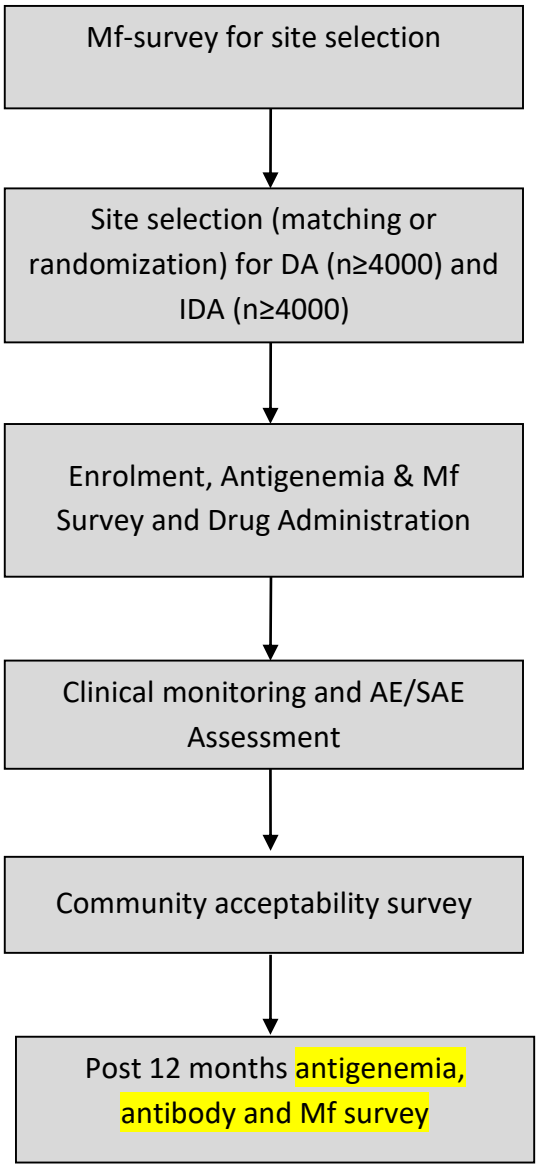
LIST OF ABBREVIATIONS

Ab	Antibody
AE	Adverse Event/Adverse Experience
AEERF	Adverse Event Evaluation and Report Form
Ag	Antigenemia
ALB	Albendazole
CRF/eCRF	Case Report Form also referred to as eCRF (electronic Case Report Form)
CRO	Contract Research Organization
DA	Diethylcarbamazine and Albendazole (Two Drug Therapy)
DEC	Diethylcarbamazine
DOT	Directly Observed Treatment
DSRB	Data Safety Review Board
IHEC	Institutional Human Ethics Committee
EDC	Electronic Data Capture
FTS	Filariasis Test Strip
GPELF	Global Programme to Eliminate Lymphatic Filariasis
GPS	Global Positioning System
ICF	Informed Consent Form
ICMR	Indian Council of Medical Research
IDA	Ivermectin, Diethylcarbamazine and Albendazole (Triple Drug Therapy)
IVM	Ivermectin
KAP	Knowledge, Attitude and Practices
LF	Lymphatic Filariasis
MDA	Mass Drug Administration
Mf	Microfilaria(e)
NTD	Neglected Tropical Diseases
SAE	Serious Adverse Event/Experience
SOP	Standard Operating Procedure
TAS	Transmission Assessment Survey
VCRC	Vector Control Research Centre
WHO	World Health Organization

1. PROTOCOL SUMMARY

Study Title	A community based study to compare the safety, efficacy and acceptability of a triple drug regimen (Ivermectin, Diethylcarbamazine and Albendazole) with a two-drug regimen (Diethylcarbamazine and Albendazole) for lymphatic filariasis elimination programme
Type of Study	Community based open intervention study
Population	IDA/ Triple Drug Arm: participants more than or equal to 5 years of age and above 15 Kg body weight DA/ Dual Drug Arm (DA): participants more than or equal to 2 years of age
Number of Treated Areas	Selected communities in Yadgir district, Karnataka based on the results of Mf survey in sentinel and spot-check sites
Duration of participation of community members	Single treatment and daily monitoring of adverse events through Day 7 Follow up for infection at 1 year post treatment.
Study Drugs	Arm 1 (Co-administration of three drugs) Ivermectin (3 mg tablets) - 200 µg /kg Diethylcarbamazine (100 mg tablets) - 6mg/kg Albendazole (400 mg tablets) - flat dose of 400 mg Arm2 (Co-administration of two drugs) Diethylcarbamazine (100 mg tablets) - 6mg/kg Albendazole (400 mg tablets) - flat dose of 400 mg
Objectives	• To determine the frequency, type and severity of adverse events following triple-drug therapy (IVM+DEC+ALB, IDA) compared to the standard two-drug treatment (DEC+ALB, DA) in infected and uninfected individuals in a community. • To compare the efficacy of IDA vs. DA administered in communities for clearance of Mf and filarial antigenemia (Ag) in cohort and effectiveness (prevalence) in community settings. • To assess and compare the prevalence of antibody (Ab) with that of Ag and Mf • To assess the presence and intensity of filarial infection on the frequency and severity of adverse events. • To compare community acceptance of MDA with IDA vs. DA.

General flow diagram



2. BACKGROUND AND RATIONALE

In 2000, WHO launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF) to eliminate lymphatic filariasis as a public health problem by 2020[1]. The National Health Policy of India2002 set the goal of achieving elimination of lymphatic filariasis (LF) in the country by 2015. The National Vector-Borne Disease Control Programme (NVBDCP) launched the programme for elimination of LF (PELF) in 2004 and adopted the WHO recommended two-drug policy of co-administration of diethylcarbamazine (DEC) and albendazole in 2007 [2]. The programme's current strategy to interrupt transmission relies on annual single dose mass drug administration (MDA) of DEC and albendazole (DA) given to the eligible population in endemic districts [3]. Disability alleviation and morbidity prevention activities include home based management of lymphoedema and surgery for hydrocele.

The programme has made significant progress with Mf levels below 1% in 222 of 255 implementation units (IUs) in 2015. Fifty-three IUs have already cleared TAS-1 while 65 IUs will conduct TAS1 and another 4 IUs are planning TAS2. Next year's round of MDA will target133 IUs. Despite this success in the majority of districts, microfilaria (Mf) levels have remained >1% in 31 "hard-core" foci (districts). The programme has been looking for additional tools to accelerate interruption of transmission in these districts and ensure that it meets the goal of elimination by 2020.

Results of a pilot study [4] (**Appendix 1a**) now confirmed with results from a clinical trial in Papua New Guinea (PNG) showed that triple drug therapy [ivermectin, DEC, albendazole (IDA)] is superior to the currently recommended two-drug regimen [5] (**Appendix 1b**) used in the global programme to eliminate LF (GPELF) outside of sub-Saharan Africa (DEC, albendazole [DA]). A single dose of IDA rapidly achieved complete clearance of *Wuchereria bancrofti* microfilariae from the blood of 12 individuals for at least one year post-treatment. All six individuals tested at 24 months were still amicrofilaraemic at that time. These results suggest that IDA permanently sterilizes adult filarial worms. Many people treated in these studies experienced transient systemic adverse events (AE) commonly associated with DEC or ivermectin treatment of filariasis, and AEs were more frequent after IDA than after DA. However, no serious adverse events (SAE) were observed in these trials or in a trial that is currently in progress in the West African country of Côte d'Ivoire. No information is available on the frequency or type of AEs following IDA treatment of uninfected persons, but this is expected to be low. The dramatic reduction and sustained decrease of mf (zero at 1 year) along with the safety profile seen in the PNG studies suggest that the triple drug therapy may be a useful tool for eliminating LF in districts in India where Mf rates have remained > 1% following MDA with the standard DA regimen. Ivermectin also provides additional benefits for recipients, because it complements the

deworming effect of albendazole and because of its effect against lice and scabies and mites. Pharmacokinetic studies done in PNG indicated no significant effect of ivermectin on DEC or albendazole drug levels [4] (**Appendix 1a**).

IDA's potential to accelerate LF elimination in India and around the world has stimulated WHO's interest as well as academic experts and the donor community. Although the studies cited above have clearly demonstrated the superiority of the IDA regimen for clearing *W. bancrofti* mf from the blood, more safety and efficacy data are needed before IDA can be rolled out on a large scale as an MDA regimen for India. WHO recommends a best practice called "cohort event monitoring" for demonstrating safety of new drug regimens for public health program use. Establishing safety for MDA through such methodology requires pre and post treatment assessment from at least 10,000 people treated across multiple settings (minimum 4000 from India). The current two-drug MDA regimens were studied in closely monitored community trials in a similar manner before they were endorsed for widespread use in the GPELF. An expanded discussion of mechanisms of action and side effects of ivermectin, DEC and albendazole is provided in **Appendix 2**. It is therefore proposed to conduct a study to acquire similar safety data in India before the new IDA regimen can be used in those districts where Mf levels have remained > 1% with the following objectives:

3. OBJECTIVES

i. To determine the frequency, type and severity of adverse events following triple-drug therapy (IVM+DEC+ALB, IDA) compared to the standard two-drug treatment (DEC+ALB, DA) in infected and uninfected individuals in a community.

ii. To compare the efficacy of IDA vs. DA administered in communities for clearance of Mf and filarial antigenemia (Ag) in cohort and effectiveness (prevalence) in community settings.

iii. To assess and compare the prevalence of antibody (Ab) with that of Ag and Mf

iv. To assess the presence and intensity of filarial infection on the frequency and severity of adverse events.

v. To compare community acceptance of MDA with IDA vs. DA.

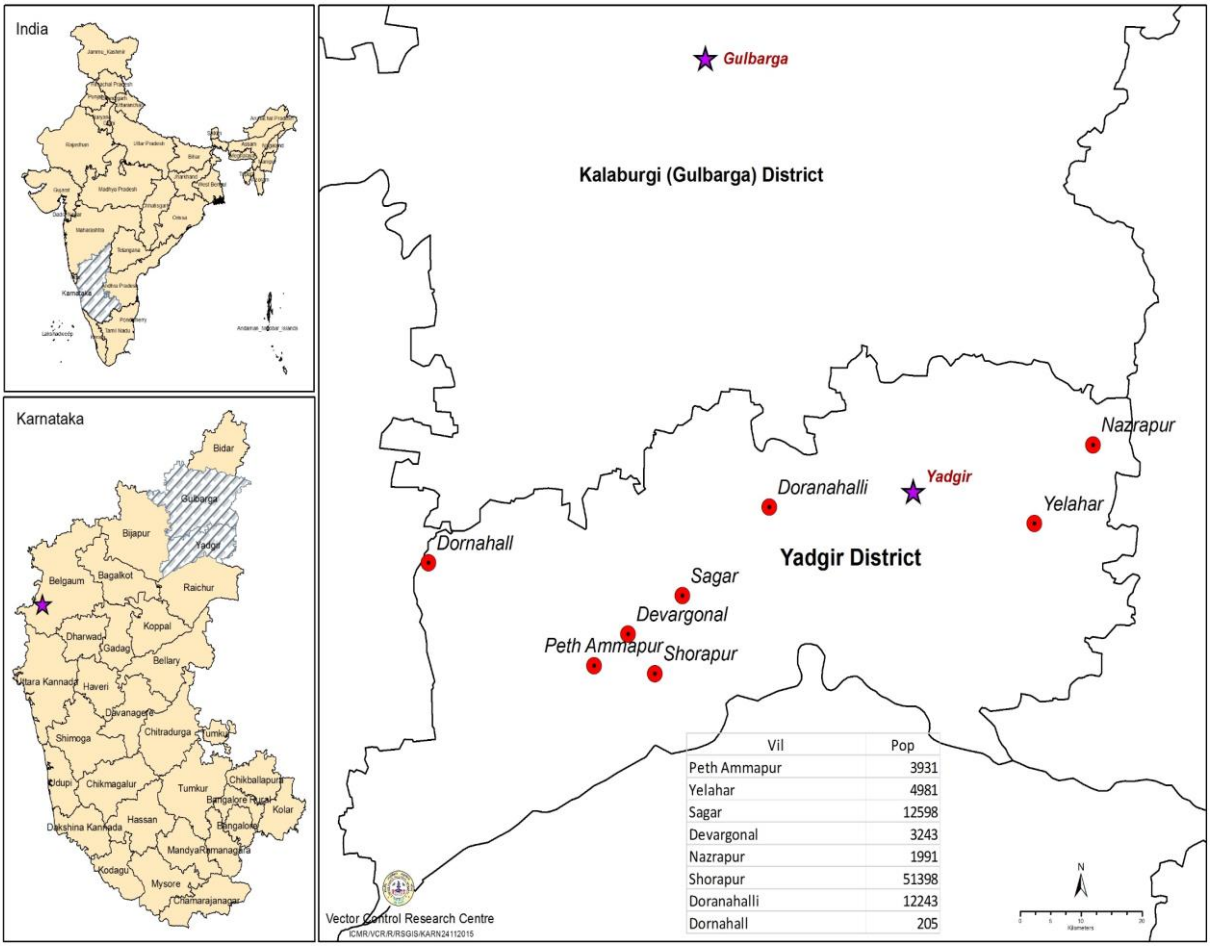
4. STUDY DESIGN

This trial will be an open labelled two-armed study. The two arms are (1) MDA with IDA (triple drug therapy) and (2) MDA with the currently used combination of DA (two-drug regimen). An overview of the study design is provided in **Appendix 3**.

4.1 Selection of study sites

The study will be conducted in Yadgir district (carved out of Gulbarga district) in Karnataka state (Map), where 12 rounds of MDA have been conducted since 2004. Mf prevalence has been shown to be persistently above 1% during annual surveys conducted by the programme. Impact assessment conducted in 2014 and 2015 (prior to 11 and 12th round of MDA) in the sentinel and spot check sites (villages) have shown many sites with >1% Mf prevalence **(Table 1)**. As the last MDA took place in Dec 2015 after the impact assessment, it is necessary to assess current prevalence of microfilaraemia to select study sites for the present study. The Mf survey will be carried out jointly by the research team and State NVBDCP as a part of impact assessment of the programme in sentinel sites as well as spot-check sites.

Map. Sites showing >1% Mf prevalence in Yadgir district, Karnataka in 2014



The minimum sample size required is 550 for a community with a population of 2000. The sample size is calculated based on an Mf prevalence of 2% with an error margin of 1% (expected prevalence is in the range of 1-3%) and 95% confidence level. Accordingly, a sample of 600 persons will be selected from each community (sentinel/ spot check sites) with a known prevalence of >2% and examined for

Mf. For this purpose, 60 µl blood will be sampled from each selected and consenting person. This way, the sites selected for the study are expected to have prevalence of at least 1% during the participant enrolment survey (pre-treatment assessment). In case, if the Mf-prevalence is less than 1% after pre-treatment assessment, additional sites will be selected based on risk ranking (line listing of LF cases) to augment the required minimum sample of 4000 in each arm.

Based on the results of the survey, the study sites will be selected and grouped into two arms of 6000 population each with comparable Mf prevalence. Sites will be assigned for MDA either by randomization or by purposive matching considering the population and prevalence of Mf. If the prevalence is homogenous across the sites, each site will be randomly assigned to one of the two treatment arms. If the prevalence is heterogeneous, sites will be selected into each arm so that the population and prevalence between the two treatment arms are similar.

4.2 Preparatory activities

4.2.1 Social mobilization

Prior to the administration of the drugs intense social mobilization activities (**Home Visit #1, Appendix 3**) will be conducted to ensure maximum community participation. Briefly, this will include development and distribution of key messages that will emphasize the acceptance and swallowing of the drugs, along with their benefits and safety. Print and electronic mass media, people-based and folk media will be used in this campaign.

4.2.2 Participant enrolment

Teams will enumerate and record the GPS coordinates of each house within the selected sites **(Home Visit #2, Appendix 3)**. Prior to enumeration, all eligible individuals will sign a written, informed consent **(Appendix 4)**. In the event that a subject is unable to read or has insufficient level of knowledge to comprehend the consent form, another villager with sufficient reading and writing skills will act a witness to the consenting process. At this time individuals will be evaluated as to whether they fulfil the inclusion/exclusion criteria, before they give informed consent. Each individual in the household will be assigned a unique barcode ID and their personal details (name, age and sex) will be entered in an enrolment e-form (**Appendix 5**). Household level information on presence of screened windows, and use of bed net will also be collected. Eligible individuals for MDA will be identified and included in the study.

4.2.3 Eligibility

All participants will provide written informed consent before any study procedures are done. Participation of minors (less than 18 years of age) will require their assent and the written consent of at least one parent.

Inclusion criteria

(i) Age ≥ 5 years and body weight above or equal to 15 Kg, male or female for IDA area and age ≥2 years for DA arm.
(ii) Able to provide informed consent or give parental consent to minors to participate in the study
(iii) No evidence of severe or systemic co-morbidities except for features of filarial disease

Exclusion criteria

Participants are ineligible to participate in the study, if they have any of the following:

(i) Age < 5 years (ivermectin is not approved for use in children less than 5 years of age) and age 5 years and above with body weight below 15 Kg for IDA arm and age < 2 years for DA arm
(ii) Pregnant women (***DEC, ivermectin and albendazole are not known to be safe for use during pregnancy***) and women of child bearing age who cannot recall the timing of their last menstrual period or who report that their last menstrual period started 4 weeks or longer before the enrolment.
(iii) Severe chronic illness (for example, chronic renal insufficiency, severe chronic liver disease or any illness that is severe enough to interfere with activities of daily living)
(iv) History of previous allergy to MDA drugs

4.3 Pre-treatment assessments

4.3.1 Health assessment

Each individual will be questioned whether they have a history or signs of LF (hydrocele, lymphedema, lymphangitis, lymphadenitis) and whether they had previous MDA for LF and the responses will be recorded in the enrolment form **(Appendix 5)**. They will also be asked whether they recently had taken albendazole or ivermectin for other conditions. If participants have any potential physical findings associated with LF they will be examined for those conditions. The study population will also have the same AE evaluation that will be used following treatment. This will include a questionnaire of subjective finding such as headache, joint pain, etc. and presence of scabies. This will establish a baseline for later assessment of AEs. Individuals will also be questioned for general health (especially

acute illness or serious chronic illness) and on last menstrual period to women participants (to establish pregnancy for women of childbearing age).

4.3.2 Screening for filarial antigenemia and microfilaraemia

All the eligible individuals in the selected community ≥5 years of age will be screened using WHO approved point-of care filarial antigen test (with approximately 75 µl blood by finger prick), and those with positive antigen test will be visited at night (8- 11 pm) for microfilaria testing (60µl measured volume thick blood smear) by finger prick method. Blood collection via finger prick is considered to be minimal risk and little or no discomfort is anticipated. The results of the tests will be recorded in the enrolment e-form **(Appendix 5).**

4.4 Drug administration

The two drug combination is a standard MDA with DEC (6mg/kg) and albendazole (flat dose of 400 mg). The triple drug administration will consist of a single dose of ivermectin (200 µg /kg) added to the standard MDA. The dosage schedule for the two drug standard MDA is given in **Table 2** and ivermectin will be based on body weight **(Table 3)**. Study personnel will directly administer the drugs. The study population will be encouraged to have food before swallowing the medicine (without chewing the tablets) with a glass of water. Vomited doses will be replaced. The study population will be informed about the active follow-ups for adverse events at 12h and 48h, and for passive evaluation up to day 7 following treatment. The drugs (quality assured) will be supplied by the companies donating for LF elimination programme and the requirement is shown in **Table 4**.

4.5 Rapid Response for management of adverse events

Medical teams will be located at strategic places. People and the drug administrators will be informed about the availability of such teams including the mobile phone numbers so that they can report directly to these teams, if necessary. These teams will be in position from the day of drug administration until the completion of mopping up operations. Each team will have an ambulance with a medical officer, a staff nurse and a pharmacist and essential life-saving drugs.

4.6 Early post-treatment assessment

4.6.1 Tiered Adverse Events Monitoring and Management

DEC, ivermectin and albendazole are known to produce adverse events in some treated persons and are self-limiting. These events can be non-specific drug related reactions which include headache,

anorexia, nausea, abdominal pain, vomiting, dizziness, weakness or lethargy. These symptoms begin within 1-2 hours of taking the drug and persist for a few hours and may disappear spontaneously with or without symptomatic treatment. Specific parasite related allergic reactions due to destruction of microfilariae and adult worms include fever, local inflammations around dead worms and pruritus.

The team that administered the drugs will visit the "treated households" for active monitoring of adverse events approximately 12 and 48 hours following drug administration. Every treated person in the community will be actively sought to have two post-treatment active event-monitoring sessions. Most adverse events, especially the more severe, occur in the first 12 - 48h following treatment associated with killing of microfilaria. However, occasional adverse events related to adult worm death may be delayed by several days. Formal assessment of adverse events (with a standard form) will take place on days 1 and 2 and later if symptoms persist or start late. To capture these late adverse events and to assure that any systemic adverse events that occurred earlier have resolved, the team will also visit study villages daily on days 3 through 7 after treatment to record any report of persistent or late-developing AEs. These evaluations will be documented by filling in pre-printed monitoring forms **(Appendix 6)** using the scoring instructions for AEs **(Appendix 6a)** and directly entered data into tablet computers using a program such as Redcap or EpiInfo.

Mild symptoms and management: In the case of mild symptomatic reactions (objective and localized: fever, lymphadenitis, scrotal pain, scrotal swelling, proteinuria, haematuria; subjective or systemic: headache, light headedness, nausea, vomiting, abdominal pain, joint pain, malaise, dizziness) local health workers/ study team will give antipyretics/analgesics and anti-allergic agents at the time of follow-up.

Moderate symptoms and management: Individuals with AEs that interfere with work or school will have more detailed assessments with a brief physical examination with measurement of temperature, blood pressure and pulse by the physician. If the initial AE monitoring reveals AEs that (a) interfere with daily activities and/or a temperature $>39^0$C (b) a significant drop in blood pressure and (c) other significant objective findings they will be evaluated for potential severe adverse event. The physician will provide any required immediate treatment and facilitate admission into the hospital or health centre, if deemed necessary. All events with grades ≥ 3 or overnight hospitalization will be referred as Severe Adverse Events that require completion of the Adverse Event Evaluation and Report Form (AEERF, **Appendix 7**)**.**

4.6.2 Severe adverse event assessment and management protocol

The study population with definite or suspected severe AEs will be referred to medical personnel for further evaluation. These evaluations will be documented with AEERF forms **(Appendix 7)**, following the instructions **(Appendix 7a)**. An independent Medical Monitor who will decide whether the AEs reported are related, possibly related, or unrelated to the treatment will review all severe adverse event assessment evaluations. Severe adverse event assessment reports will be sent electronically to the Independent Medical Monitor (who has received GCP training and is experienced in clinical trials and management of AEs following treatment of lymphatic filariasis). Classification of events as Serious Adverse Events and causation (definitely related to MDA, probably, possible, or unrelated) will be based on the attending physician's report and the medical monitor's opinion. Medical monitor will forward severe adverse event assessment reports to the data safety review board. Individuals with severe adverse events (whether related or unrelated to drug treatment) will be hospitalized if necessary and followed until their symptoms have resolved. All severe adverse events will be reported within 48 hours. The report will be submitted to the Chairperson of DSRB nominated by Govt. of India within 7 days and the Institutional Humans Ethics Committee (IHEC). Server Adverse event is considered as serious adverse event/experience (SAE) when the severity grade is 4 and above.

4.6.3 Compensation for Injury

The study drugs have been widely used for treatment of lymphatic filariasis and it is anticipated that injury resulting from treatment will be rare. In the event that a participant experiences severe adverse event attributable to study treatment, expenses towards medical treatment and/or hospitalization will be covered through medical insurance. Participants reporting with severe adverse events in the grade 5 will be covered under liability insurance policy.

4.7 Data safety review board (DSRB)

The DSRB will monitor the type and frequency of AEs and SAEs recorded by the teams and provide guidance to the teams in the field. The DSRB and the Institutional Humans Ethics Committee (IHEC) may conduct a review after MDA was distributed to 500 people in each treatment area and to consider stopping the study if 5 or more of 500 people experienced SAEs attributable to MDA.

4.8 Acceptability of triple drug regimen

Community acceptance will be measured by surveying community members receiving either the 2-drug or 3-drug regimens. A survey questionnaire will be designed, pre-tested and used to assess what

respondents know about LF, what they think of people with LF, how do they perceive LF affects their health, how the health system manages people with LF, especially their perceptions on study drug administration and of reactions to treatment and fears of being treated. The sample will include two categories of individuals: (i) Mf and Ag positive and (ii) Mf and Ag negative. In estimating the sample size for the acceptability survey, estimated acceptability rates are available only for 2-drug regimen. In the absence of such information for 3-drug acceptability rate, the difference in the estimate that may be expected between the regimen groups cannot be derived for estimating the sample size. As a result, this survey will create preliminary data, providing an insight into possible trends in acceptability. Therefore, a minimum of 100 individuals above 14 years will be randomly selected in each category for the survey in each arm. All the Mf and Ag positive individuals (above 14 years) will be included if the number is below 100.

To complement this survey, a series of focus group discussions (FGD) in the community as well as key informant interviews (community leaders, health personnel and drug distributors in the same communities) to assess perceptions about the 3-drug versus the 2-drug regimen will be conducted at the same time along with community survey. Persons from specific groups of people such as women of reproductive age, young people, men and community health workers will be included in the FGD to understand their perspectives on DOT, AE and messaging for the 3-drug regimen. A purposive sampling frame will be used, with individuals identified based on their leadership and cultural position with the village as well as their involvement with LF elimination and with the community trial. A range of 8-10 individuals will be included from each arm.

Guidelines for developing questionnaire for community acceptability survey, Key informant interview and focus group discussion are given in **Appendix 8**.

4.9 One year post-MDA assessment

4.9.1 Effectiveness of IDA versus DA

Effectiveness will be assessed by comparing the pre and 12 months post-MDA prevalence of Mf and Ag, and intensity of Mf between the two arms, by testing a cross section of the population in each arm. Finger prick blood sample measuring 75 µl, and six blood spots (120 µl), each with 20 µl blood on a filter paper for detecting Ag and antibody (Ab) respectively will be collected from the consenting individuals in the selected households between 1700 and 2100 hrs by door to door visit. FTS will be used for detecting Ag and Wb123 or Bm14 will be used for Ab. All Ag-positives will be further blood

smeared for Mf between 2100 and 2300 hrs on the same day. All samples will be processed following respective SOPs for FTS, antibody and Mf.

4.9.2 Efficacy of IDA versus DA

For assessing efficacy, individuals who were positive for either Mf or Ag, prior to MDA will be re-examined for both Mf and Ag, and also for Ab. A fraction of positive cohorts (Ag and Mf) are expected to be covered under the effectiveness survey. If required, special efforts will be made to cover more positive cohorts by visiting their households.

4.10 Treatment

Person positive for Ag or Mf will be treated with the 3-drug regimen (Ivermectin, DEC and albendazole).

4.11 Data Collection

4.11.1 Pre-treatment

Data will be collected using tablet-based systems, which will be pre-loaded with appropriate software. Field teams will be trained in the use of the instruments and data will be uploaded as soon as entries are completed. The secondary data available on other characteristics of the population such as migratory pattern, prevalence of co-morbid conditions and malnutrition status will be collected. Information on the vectors and transmission parameters will be collected.

4.11.2 Post-treatment

The 12-month post-MDA survey for both efficacy and effectiveness assessment will carried out simultaneously. For the effectiveness study, a database developed in EPIINFO software (CDC, Atlanta) will be used to capture data using Android based mobile phones, excluding all positive persons in the cohort. The data for the cohort will also be captured using tablet-based electronic data capturing (EDC) system that was developed and used during pre-MDA survey. The details of all individuals in the cohort will be pre-loaded and used to capture data during the 12-month post-MDA survey.

5. STATISTICAL CONSIDERATIONS

5.1 Safety data

The sample size of ≥4000 in each arm is sufficient to test the hypothesis that the rates of severe AEs following IDA or DA are less than 0.1%. It is well known that systemic AEs are related to killing of Mf and that the severity of AEs is related to Mf counts. Since Mf rates in villages in the study area are

relatively low, the study will not be powered to compare rates of SAEs by MDA regimen. The primary endpoint for safety studies will be the rates of SAEs that occur in infected and in uninfected subjects within the first 7 days post MDA.

5.2 Effectiveness

With a pre-MDA Mf prevalence of ~6% in each arm, the Mf prevalence is expected to be ~2% 12-months post-MDA considering a coverage of 70% under MDA. Assuming both IDA and DA are equivalent ('equivalence trial') in clearing infection and that a difference of 1.2% in infection prevalence is considered as equivalent, a sample of 3600 individuals per arm is sufficient to compare the effectiveness between the arms. This sample size has 80% power of detecting the true difference of more than 1.2% and no more than 5% chance of falsely concluding that the difference is less than 1.2% when in fact it is more than 1.2%. The sample size was adjusted for a design effect of 1.5 and a non-response rate of 10%. With an average family size of 5, a total of 720 households per arm need to be selected following systematic sampling method. All the consenting individuals aged five and above will be tested for filarial infection in both the arms.

5.3 Efficacy

Assuming an Mf-prevalence of 1% in the study population at baseline, the survey is expected to detect at least 60 Mf positives in each arm. A minimum of 35 of these Mf-positives in each arm will be retested at 12 months post-treatment for antigenemia and microfilaraemia. This sample size is adequate to demonstrate superiority of the IDA regimen (assumptions: 90% reduction in Mf-prevalence after IDA and 60% reduction after DA, 80% power for detecting an effect size of 30%). The primary endpoint for efficacy will be complete clearance of Mf 12 months post MDA. Another secondary endpoint will be clearance of filarial antigenemia at 12 months post MDA.

5.4 Assessing prevalence of antibody

For assessing the prevalence of antibody, a minimum sample size of 800 per arm was estimated. This was arrived at by assuming an antibody prevalence of 25%, with 3% error margin and 95% confidence level. As the sampling unit is a household, the sample size is adjusted for a design effect of 1.5 and therefore a total of 1250 individuals need to be surveyed. Assuming an average family size of 5, a total of 250 households need to be surveyed and all the persons volunteering to participate in the selected household will be included in the sample. This sample can be achieved by selecting every 3rd house of the 720 households covered for filarial infection in each of the arms.

5.5 Follow-up of pre-MDA positives

From human ethics point of view, all the Ag positive (1263 in IDA and 1031 in DA arms) and Mf positive (326 in IDA and 265 in DA arms) individuals detected during enrolment are required to be retested for their current infection status. Therefore those Ag/Mf positives not covered under the effectiveness/efficacy surveys will be approached and if available will be tested for Ag and Ab. Ag positives individuals will be further tested for Mf.

6. BIOHAZARD CONTAINMENT

Universal precautions for people collecting blood and working with blood samples and proper disposal of contaminated materials (test strips, lancets, capillary tubes, blood film slides) will be adhered in accordance with the guidelines prescribed by the local health authorities.

7. DISSEMINATION ACTIVITIES

A dissemination workshop will be held after the results are available to inform other stakeholders. The results will be published in an open access peer reviewed journal.

8. TEAM COMPOSITION AND WORK PLAN

(i) A Social Scientist assisted by a Junior Social Worker, PHC level health educator and community liaison persons will be involved in each arm to carry out social mobilization activities in the preparatory phase of the study. This activity will precede participant enrolment. The sociologist team will approach the households, carry out campaigns and prepare the community for the MDA. Each team is expected to complete 140 houses every week. The sociology teams will also be involved in assessing the acceptability using community survey, FGD and KI interviews after the completion of drug administration within the recall period of one month.

(ii) Another team of six members (one physician, two laboratory technicians one each for sample collection and reading antigen test results, one junior nurse, one data entry operator and one field assistant) will be responsible for the following activities: consenting, enumeration, pre-treatment assessments, drug administration and post-treatment AE assessments. The drug distributor in the routine MDA programme in the villages and/or community liaison persons will be a part of the team. There will be 7 such teams in each arm of the study. Each team will visit

the house, get the consent from the members, assess pre-treatment health status, screen all the available individuals for filarial antigenemia and administer drugs except those who are positive for antigenemia. Antigen positive individuals will be tested for microfilaraemia by collecting night blood sample after 9.00 PM and then treated.

(iii) A team is expected to complete 8-10 households (~40 individuals) in a day. During the first door to door visit, the team will enrol the participants, assess health parameters, screen the individuals for filarial infection and provide directly observed treatment. The team will revisit the "treated households" for active monitoring of adverse events if any, to manage the AEs on day 1 and 2 post treatment. Once these activities are completed in these houses, the team will move on to the next batch of 10 houses. A team is expected to cover 16-20 households in a week. All the data pertaining to these activities will be entered in the e-formats by the DEO in the field itself. In this process, a minimum 8-10 weeks is necessary to cover the target population in both the arms (refer section 9). A team with similar composition will be formed for assessing Ag and Mf prevalence after 12 months post treatment and to treat the positive cases.

(iv) A separate team of a physician and a junior nurse will passively monitor the treated individuals (20 - 30 households in a day) for an extended period of 7 days following the treatment in each arm. This team will be supported by the existing Rapid Response Team (RRT) in the District monitoring and managing the AEs in both the arms.

(v) The Medical Officer(s) and Health Inspectors in the PHCs of respective arms will assist the investigators in co-ordinating the activities of the team in the villages and referrals. At the District level, the District Health officer (DHO) and the District Vector Borne Disease Control Officer (DVBDCO) will provide assistance in selection and organisation of teams for various activities including the PHC staff and conducting training programmes and overall supervision. The District Health officer will provide support in terms of deploying the Rapid Response Team, referral arrangements and Hospital support.

(vi) There will be an independent Medical Monitor who will receive severe adverse event assessment reports electronically from the attending physician and forward the report with opinion to the DSRB through the PI/Co-PI.

(vii) All the members of the teams who have basic medical skills will be trained on AE evaluations. Laboratory Technicians will be trained on blood sampling, smearing, processing and examination

of slides for Mf, and reading of antigen test results. Hands on training will be given to the data entry operators on geo-referencing the households and filling up of e-forms using e-tablets pre-loaded with appropriate software.

9. TIMELINE OF ACTIVITIES

Activities and time line

S.No.	Activity	Target	No. of Teams	No. of person / team	Max Days	Jul-16				Aug-16				Sep-16				Oct-16				Nov-16				Dec 2016 - Nov 2017	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18
						W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4		W1-W4	W1-W4	W1-W4	W1-W4	W1-W4	W1-W4
$1	Staff Recruitment and training				20	Recruitment																					Recruitment					
$2	Pre screening for Mf for site selection	4000	8	3	12			DHO	DHO																							
$3	Selection of study sites and advocay																															
$4	Preparation of IEC and training the field teams																															
$5	Social mobilization for screening and drug distribution	2400 HHS	2	2	66							B	B	B	B	B	B	B	B	B	B	B	B									
$6	Sensitization and training for Rapid Response team				7						DHO																					
$7	1. Patient enrolment (i) Obtaining consent (ii) Pre-MDA health assessment (iii) Screening - Ag (iv) MF screening 2. Drug Distribution 3. Adverse Events Survey (active) 3. Adverse Events Survey (passive)	2400 HHS	15	6	60							A	A	A	A	A	A	A	A	A	A	A	A	A								
$8	Rapid Response team visits											DHO	DHO	DHO	DHO	DHO	DHO	DHO	DHO	DHO	DHO	DHO	DHO	DHO								
$9	Post-Treatment Survey - Acceptability	400 persons	2	2	30																			B	B							
$10	Post (12 M) -Treatment assessment - Mf and Ag survey	2400 HHS	15	2	19																						C	C	C	C	C	
$11	Slide processing and examination	990 Agpos	1	3	20																						C	C	C	C	C	
$12	Data analysis and report writing																															

Team composition

Team A : Physician(1no.); Technician C (3nos.: 1 for blood sampling, 1 for FTS reading and 1 for Data entry); Nurse/Field Worker (1no.) Field Assistants (1no.)

Team B : Sociologist (1); Junior Social Worker (1)

Team C: Technician C (2no.); Field Worker (1no.); Field Assistant 1no.); DEO (1no.)

DHO : Distirct Health Officials

10. BUDGET

Budget Heads	Amount in INR	Amount in USD
Personnel	₹ 238,38,293.00	$3,50,929.54
Field allowances	₹ 10,80,000.00	$15,898.95
Equipment	₹ 15,22,500.00	$22,413.11
Supplies	₹ 4,02,000.00	$5,917.94
Contingency	₹ 2,80,400.00	$4,127.84
Mobility	₹ 36,00,000.00	$52,996.51
Communication	₹ 1,26,000.00	$1,854.88
Field lab	₹ 15,84,000.00	$23,318.46
Miscellaneous (Insurance policy)	₹ 2,14,700.00	$3,160.65
Review and steering committee meetings (ICMR)	₹ 12,58,200.00	$18,522.28
	₹ 339,06,093.00	$4,99,140.18

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Table 1 Mf prevalence in sentinel and spot check sites in Yadgir district in 2014 and 2015

PHC	Sub-centre	Village	Type	Population	Mf % (2014)	Mf % (2015)
Dornalli	Dornalli	Doranahalli	Sentinel	1369	5.38	3.09
Konkal	Nazarpur	Nazarpur	Sentinel	2131	2.20	1.18
Petammapur	Petammapur	Petammapur	Sentinel	3820	1.90	3.30
GGH Shorapur	Shorapur	Ranganpet	Sentinel	707	1.97	0.40
Yelheri	Yelheri	Yelheri	Spot-check	3575	2.53	ND
Sagar	Sagar	Sagar	Spot-check	6391	2.95	ND
Devargonal	Devargonal	Devargonal	Spot-check	3300	3.00	ND
Yadgir urban	NA	Kalachaputra	Spot-check	NA	0.58	ND
Shahapur	Shahapur	Shahapur town	Spot-check	NA	ND	1.38
Kandakur	NA	Gunjanur	Spot-check	NA	ND	0.79
Yeleri	NA	Kaladelagundi	Spot-check	NA	ND	0.92
Chattanahalli	NA	Khanapur	Spot-check	NA	ND	1.65

NA: Not available
ND: Not done

Table 2 Drug dosage for DA arm (as per national Guidelines)

Age (Years)	DEC		Albendazole	
	Dose (mg)	No. of 100 mg tablets	Dose (mg)	No. of 400 mg tablets
Less than 2	0	0	0	0
2 - 5	100	1	400	1
6 - 14	200	2	400	1
15 +	300	3	400	1

Table 3 Weight based dosage for ivermectin (all persons of age > 5 years with weight ≥ 15 Kg)

Weight (kg)	Ivermectin (mg)	No. tablets (3 mg)	**Rounded No. tablets (3 mg)**
< 15	1.8	0.6	**0**
15	3.0	1.0	
16	3.2	1.1	
17	3.4	1.1	
18	3.6	1.2	
19	3.8	1.3	**1**
20	4.0	1.3	
21	4.2	1.4	
22	4.4	1.5	
23	4.6	1.5	
24	4.8	1.6	
25	5.0	1.7	
26	5.2	1.7	
27	5.4	1.8	
28	5.6	1.9	
29	5.8	1.9	
30	6.0	2.0	
31	6.2	2.1	**2**
32	6.4	2.1	
33	6.6	2.2	
34	6.8	2.3	
35	7.0	2.3	
36	7.2	2.4	
37	7.4	2.5	
38	7.6	2.5	

Weight (kg)	Ivermectin (mg)	No. tablets (3 mg)	**Rounded No. tablets (3 mg)**
39	7.8	2.6	
40	8.0	2.7	
41	8.2	2.7	
42	8.4	2.8	
43	8.6	2.9	
44	8.8	2.9	
45	9.0	3.0	
46	9.2	3.1	**3**
47	9.4	3.1	
48	9.6	3.2	
49	9.8	3.3	
50	10.0	3.3	
51	10.2	3.4	
52	10.4	3.5	
53	10.6	3.5	
54	10.8	3.6	
55	11.0	3.7	
56	11.2	3.7	
57	11.4	3.8	
58	11.6	3.9	
59	11.8	3.9	
60	12.0	4.0	**4**
61	12.2	4.1	
62	12.4	4.1	
63	12.6	4.2	
64	12.8	4.3	
65	13.0	4.3	
66	13.2	4.4	
≥67	13.4	4.5	

Table 4 Drug requirements for the two arms, IDA and DA

Drug	Age group (Years)	Population	No. of tablets per person	Total no. Tablets	Additional tablets *	Grand total (Tablets)
DEC 100 mg	All > 2 years	12000	2.5	30000	7500	37500
Albendazole 400 mg	All > 2 years	12000	1	12000	3000	15000
Ivermectin 3mg#	All >5 years	6000	1-4*	21600	5400	27000

Based on 200 µg per Kg body weight

* Required for retreatment of positives and marginal increase in population size during the selection of villages