An advanced cookstove intervention to prevent pneumonia in children under 5 years old in Malawi: a cluster randomised controlled trial

Protocol

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Trial personnel

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TRIAL PARTNERS

This proposal benefits from 2 public-private partnerships that will be key to the successful conduct of the trial, influencing public policy and the sustainable scale-up of the intervention in the future.

African Clean Energy (ACE) is a Lesotho-based company that has built an industrial scale manufacturing plant in Lesotho as a joint venture with Philips to produce the advanced cookstove we are using as our intervention. Through our partnership with ACE we will have a secure source of the Philips cookstove for the trial. The locally relevant business knowledge that ACE brings, together with the planned economic and qualitative work, will help to plan the up-scaling of the intervention if indicated in the future. ACE has committed to provide these stoves at the lowest possible cost for the trial and up-scaling.

Aprovecho Research Centre (ARC) (www.aprovecho.org) is a not for profit corporation that carries out research, develops and disseminates clean cookstove and other energy technologies. ARC has implemented over 2 million improved cooking and heating stoves around the world. ARC has helped to inform the selection of our intervention and will play a key role in the dissemination of the trial findings to the cookstove research and implementation programme communities.

EXECUTIVE SUMMARY

Background: 700 million people in Africa burn biomass to provide energy for cooking, heating and lighting. The smoke this generates causes considerable morbidity and mortality (4 million deaths a year worldwide). Pneumonia in the under 5s is one of the major diseases associated with biomass smoke exposure and a serious cause of avoidable mortality in less developed countries. There are now efficient biomass-burning cookstoves that substantially reduce smoke emissions and exposures. This trial will evaluate whether provision of an advanced cookstove (Philips fan assisted stove) will reduce pneumonia in young children.

Design: Village-level cluster randomised controlled trial with two arms of equal size.

Population: Children up to 4½ years old in Malawi allowing for a minimum of 6 months data collection before a child's 5th birthday.

Intervention: The Philips fan assisted stove with user training (replacing open fires).

Control: Continuation of traditional cooking methods (open fire).

Primary Outcome: Incidence of pneumonia in children under 5 years of age. Diagnosis made by physicians blinded to trial arm using the WHO Integrated Management of Childhood Illness (IMCI) pneumonia assessment protocol.

Time: 24 months follow up.

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INTRODUCTION

The problem to be addressed

Malawi has one of the world's highest infant and under five mortality rates (69 and 110 per 1000 live births respectively in 2009) despite having made progress towards meeting the Millennium Development Goal of reducing child mortality (1). Pneumonia is the leading cause of death and one of the commonest causes of morbidity. Malawi Ministry of Health (MoH) and World Health Organization (WHO) estimate around 300 per 1000 children under the age of 5 are diagnosed with pneumonia every year with a case fatality rate between 2.7 and 13.2 per 1000 (2,3). Exposure to smoke produced when biomass fuels (animal or plant material) are burned in open fires is a major avoidable risk factor for pneumonia (4, 5). In Malawi, where at least 95% of households depend on biomass as their main source of fuel and household air pollution levels are high (6), biomass smoke exposure is likely to be responsible for a substantial burden of this disease (4,5).

Why a trial is needed now and why is it needed in the proposed location

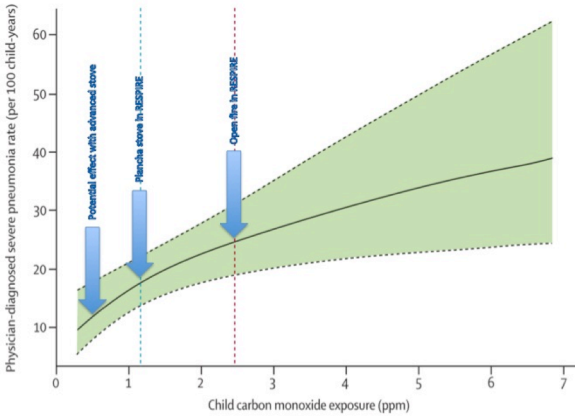
700 million people in Africa use biomass fuel to provide energy for cooking, heating and lighting. Women and young children experience high levels of smoke exposure when meals are cooked over open fires in the home due to partial combustion of fuel and poor ventilation (5). Household air pollution from open fires is a major threat to health, ranking 10th in the WHO comparative risk assessment for the global burden of disease (7). WHO estimates 4 million premature deaths are caused by household air pollution worldwide every year. Around half a million of these deaths are due to pneumonia in young children (7, 8). Other adverse health effects associated with biomass smoke exposure include stillbirth, low birth weight, chronic obstructive pulmonary disease and lung cancer (5, 9-11). Effective strategies for reducing both biomass fuel consumption and smoke exposure include improved stoves, ventilation, cleaner fuels and behaviour modification. Some of the more advanced biomass-burning cookstoves reduce emissions by as much as 90% by incorporating technologies (*e.g.* fans) that improve combustion efficiency (12). Access to smoke exposure reduction technologies is limited by poverty in much of the developing world. The Global Alliance for Clean Cookstoves (GACC) was launched in 2010 to tackle the lack of access to clean affordable energy through public-private partnerships (http://cleancookstoves.org/). A central aim of the alliance is for 100 million homes to adopt clean and efficient stoves and fuels by 2020. There is, however, very limited evidence to assess the potential health benefits of such an approach. A trial is needed now in Africa to deliver relevant and timely evidence about the health and economic impacts seen when households adopt advanced cookstove technologies to impact on communities and policy makers.

Relevant systematic reviews and the need for this trial in light of these reviews

We have published a systematic review and meta-analysis of the literature relating to indoor air pollution from unprocessed solid fuel use and increased pneumonia risk in children below 5 years of age (8). We calculated an overall pooled odds ratio (OR) of 1.78 (95% CI 1.45-2.18) for the association between solid fuel use and pneumonia using data from 24 studies. A more recent estimate from Po *et al* (13) suggests a higher OR of 3.52 (95% CI 1.94-6.43). This substantial increased risk of pneumonia in young children in relation to unprocessed solid fuel use calls for intervention studies to identify effective and cost effective approaches to reduce this risk.

How the proposed trial will differ from or complement any relevant planned, ongoing or recently completed trials internationally

Only two trials have been carried out anywhere in the world (Mexico and Guatemala) to evaluate the effects of biomass smoke exposure reduction interventions on health outcomes (14, 15). Both trials used stoves that reduce exposure mainly by venting emissions to the outdoor environment with a chimney rather than by improving combustion efficiency. Romieu *et al* compared a Patsari stove intervention with traditional open fire on respiratory symptoms and lung function in 552 women in Mexico (14). Adherence to the intervention was poor (50%) but the Patsari stove reduced respiratory symptoms (*e.g.*rate ratio (RR) 0.29 (95% CI 0.11-0.77) for wheeze) and lung function decline (31ml *vs* 62ml over 1 year, p=0.01) in those who used the stove. The RESPIRE trial randomised 534 households with a pregnant woman or infant in highland Guatemala to a Plancha stove or open fire and assessed the impact on pneumonia in children <18 months (15). The Plancha gave a non-significant reduction in incidence of physician-diagnosed pneumonia (primary outcome) with a RR of 0.84, 95% CI 0.63-1.13, p=0.26 (after multiple imputation RR 0.78, 95% CI 0.59-1.06, p=0.10) and a significant reduction in physician-diagnosed severe pneumonia (RR 0.67, 95% CI 0.45-0.98, p=0.04) despite only a 50% reduction in personal smoke and carbon monoxide exposures and an improvement in household air pollution to levels still well above WHO recommended limits. An exposure-response relationship was seen between biomass smoke exposure and pneumonia risk with the risk rising steeply at low levels and flattening off at higher levels of exposure (figure).



The Current Controlled Trials database was searched across all registers using search terms 'biomass', 'stove', 'cookstove' in February 2012. The only relevant trial currently ongoing or planned for a site in Africa will evaluate birth weight and acute lower respiratory tract infection (ALRI) within the first few months of life in Ghana (NCT01335490). We have reviewed the protocol for this trial; this will generate complementary results to ours. One trial of an improved cookstove with ventilation is ongoing in Nepal with ALRI and birth weight outcomes (NCT00786877). There is a striking lack of existing and planned clinical trials evaluating the impact of biomass smoke exposure reduction interventions on health outcomes in Africa. The proposed trial will address an important gap in the clinical trials evidence base by determining whether an advanced cookstove intervention that is expected to reduce smoke exposure to levels well below those seen in RESPIRE can prevent pneumonia in African children under the age of 5.

PRELIMINARY WORK

We have conducted an exploratory randomised controlled trial of a cookstove intervention in Ntcheu, Malawi (PACTR201110000324321). The main focus of this work was to evaluate methodological issues of direct and practical relevance to this proposal. Findings include: 1) we saw high levels of interest from villagers in participating in the trial and active support from village elders and other community leaders such that 1 field worker was able to recruit 51 households from 5 villages over 5 visits; 2) the outcome measurements used (questionnaires, exhaled carbon monoxide, oxygen saturations, carbon monoxide exposure) were acceptable although 2 participants withdrew because of superstitious beliefs about HIV and oxygen in relation to these assessments. Superstitions and misbeliefs are not uncommon in Malawi and will be tackled in the proposed trial through careful community engagement exercises. We will also explore these issues through qualitative work described in a later section.

TRIAL DESIGN

Village-level cluster randomised controlled open trial with two arms of equal size.

RESEARCH QUESTIONS

1) Can an advanced cookstove intervention that substantially reduces biomass smoke exposure relative to an open fire prevent pneumonia in children under 5 years old in Malawi?

2) What is the association between exposure to household air pollution (carbon monoxide) and the development of pneumonia in children under the age of 5 in rural Malawi?

3) What is the prevalence and determinants of obstructive lung disease in adults in rural Malawi and to what extent does exposure to household air pollution explain the rate of decline in lung function in adults in rural Malawi?

4) How affordable and cost effective is the intervention from household, healthcare system and societal perspectives?

5) What can be learned from trial participants and non-participants about adoption of the intervention that could inform effective implementation of the trial findings in the future?

TRIAL POPULATION

Trial sites

The trial will benefit from strong support from the Malawi Liverpool Wellcome (MLW) Programme, a major overseas programme of the Wellcome Trust and research unit within the College of Medicine (COM), University of Malawi (http://www.mlw.medcol.mw). MLW will provide a central hub for the trial, infrastructural and administrative support. We will initiate the trial through the MLW Chikhwawa field site and one other major research centre in Karonga.The Chikhwawa field site has been selected in light of the key strategic research importance of this site, the relevance of this proposal to the MLW Child Survival Initiative in Chikhwawa and the opportunities for this trial to benefit from an existing Wellcome Trust investment whilst providing added value to this research field site through capacity building (including specific clinical trials training) and infrastructure development. The Karonga centre has been selected given the successful implementation of many other research projects at this site, access through this centre to established infrastructure, logistical support and experienced field staff. The sites both benefit from having a District Hospital that trial participants will attend in the event of illness. We anticipate being able to recruit a sufficient number of villages and households through these centres. We have links with other sites in Mulanje that could be opened if needed.

Inclusion/exclusion criteria

We will include children up to 4½ years old in Malawi because of the high burden of morbidity and mortality from pneumonia in the under 5s and to ensure a minimum of 6 months data collection before a child's 5th birthday. Households with children under 4½ will be recruited from Chikhwawa, and Karonga.To maximise generalisability of the findings the trial will be broadly inclusive and open to all consenting households with a child under 4½ (including households where babies are born during the trial). Children known to have HIV (around 5%) will be eligible for inclusion.

Households with at least one adult aged 18 years or older will be eligible for inclusion in the sub studies involving adult participants.

Sources of recruitment

An initial mapping exercise will be conducted to identify 150 suitable village level clusters across Chikhwawa and Karonga. A community engagement exercise will be carried out simultaneously to seek community leader and villager support for the trial (including careful discussion about the importance of having a control group and the chance of being a control village).

Following allocation to intervention or control group, field workers will visit each village to recruit individual households to the trial. We will include approximately 4012 households (with an average of 2.5 eligible children each) from 150 village level clusters. From our exploratory RCT in Ntcheu we found that one field worker could recruit and obtain baseline data from an average of 10 participating households in one day. Recruitment will therefore require about 530 full days of fieldwork. With 15 fieldworkers working at a maximal rate for 5 days a week this work would take 7 weeks. A more realistic timescale is 6 months that will allow for preparatory work for field visits, community engagement, training and distribution of cookstoves, illness, leave and logistical challenges.

ALLOCATION OF INTERVENTIONS

Within each district, villages that have agreed to participate will be randomly allocated to the intervention and control arms using a computer-generated randomisation schedule with stratification by site, distance from (or accessibility to) health centre and size of cluster.
This randomisation will be performed by the trial statistician using dummy codes “A” and “B” only to represent intervention and control groups; to ensure the statistician remains blinded, the identity (allocation) of “A” and “B” will be determined by a person independent of the study. Within each village all households with children up to 4½ years old will be invited to participate. After informed consent has been given by a member of the household with authority to do so, the household will be enrolled and given a Household Trial Number; each child in the household will be given a Participant Trial Number linked to the household number.

The interventions

Experimental arm –The Philips fan assisted stove with user training (replacing open fires). The Philips stove is an advanced cookstove technology that incorporates a fan to improve combustion efficiency and reduce smoke emissions by 90% (12). The stove has undergone vigorous laboratory and field evaluation by our trial partners. This work provides confidence that the Philips stove is a suitable intervention for emissions reduction, robust and acceptable to the end user. The need to charge the battery that powers the fan from time to time has not been a barrier to adoption during our pilot work; the stoves will be supplied with solar charging solutions. We will provide two stoves to each household since the ability to cook using only one pot at a time was seen as a disadvantage of the Philips stove compared to the open fire in our preparatory work.

Control arm – Continuation of traditional cooking methods (open fire). Control households will be offered two Philips stoves at the end of their period of participation in the study in the interests of fairness and to help achieve high levels of post-recruitment retention.

The duration of treatment period
The intervention and follow-up period for included households will be 24 months.

OUTCOME ASSESSMENT

Outcome measures

Primary: Incidence of IMCI defined pneumonia in children under 5 years of age.

Secondary efficacy: Incidence of all pneumonia (including those not meeting IMCI criteria), severe pneumonia and death in children under 5 years of age. We will also assess respiratory symptoms and burns, conduct spirometry (adult members of households only), household air pollution and personal exposure, measure cookstove use and conduct economic and health service evaluations.

The frequency and duration of follow-up

Fieldworkers will visit included villages every 3 months for 2 years to collect primary and secondary outcome data, repair/replace cookstoves and mobile phones if necessary and troubleshoot. This will be backed up by telephone contact with a village representative every 4 weeks.

How the outcome measures will be measured at follow up

Primary outcome case definition: Pneumonia in children under 5 years of age will be diagnosed by physicians, medical officers or other appropriately trained staff at local healthcare facilities, blinded to intervention allocation. The WHO IMCI pneumonia assessment protocol (16) will be used to make the diagnosis since chest X-rays are not universally available in the study areas. Briefly, pneumonia is diagnosed using the IMCI protocol by the presence of cough or difficult breathing and signs of pneumonia - fast breathing (60, 50 or 40 breaths per minute or more in those <2 months, 2-12 months and 1-5 years respectively), chest in-drawing, stridor or any general danger sign (inability to drink or breastfeed, vomiting, convulsions, being lethargic or unconscious). Severe IMCI pneumonia is identified by the presence of any general danger sign, chest wall in-drawing or stridor in a calm child. Oxygen saturation <90% will be included as an additional and objective marker of severity. Where available, additional data supporting the diagnosis of pneumonia (e.g. presence of pyrexia, chest X-ray findings) will be collected. The clinical information recorded in health passports used to make each diagnosis of pneumonia and assess its severity will be subject to review by a fully blinded Independent Endpoint Review Committee comprising 3 paediatric specialists not otherwise involved with the trial. A further level of pneumonia diagnosis validation will be possible at the Chikhwawa field site by capitalising on the improved diagnostics (e.g. blood cultures) being developed by MLW at this site. Pneumonia diagnoses made within a month of each other will be counted as the same episode but otherwise as separate episodes. We will record all deaths and try to distinguish deaths due to pneumonia from other causes. If a child dies at home and it is acceptable to do so, we will undertake verbal autopsies.

Practical details: Clinical assessment and treatment at the local health facilities will be based on clinical need and conducted by independent physicians or medical officers blinded to allocation. A supply of antibiotics that reflects local prescribing practice for pneumonia will be provided to local health facilities for use if antibiotics are indicated but would otherwise be unavailable. We will support local health services to achieve high quality clinical assessments and documentation of pneumonia diagnoses, severity assessment and ensure the trial does not present a burden on these services. In addition to educational and trial promotion exercises we will facilitate high quality assessments and documentation by providing all trial participants with a new health passport if they do not currently have one with a sufficient number of blank pages. These are medical records which patients in Malawi keep. A sticker will be inserted in the passport explaining that the patient is in a trial with a brief summary of the IMCI pneumonia assessment protocol and boxes to tick if the patient is diagnosed with pneumonia and if so whether this was severe or not. Malaria will be tested for (at the study sites a rapid diagnostic test is generally used) and treated as indicated as part of routine clinical practice and the result of this recorded in the health passport. During or after the attendance, the trial team will be notified by text or phone call about

the event by health facility-based staff or a member of the household using a phone and airtime credit provided to a nominated CAPS village representative. Deaths will be reported in the same way. Fieldworkers will review the health passports of all children in the trial at 3-monthly visits to the villages to obtain information about episodes of pneumonia and deaths not otherwise detected by this system.

Secondary outcomes: We will include assessment of respiratory symptoms, burns and lung function as secondary outcomes. We will do this by active surveillance in the villages every 3 months using respiratory symptoms and burns questionnaires and every 12 months using spirometry (up to 2000 adult members of households across the CAPS trial sites). There is a dedicated burns unit at the Queen Elizabeth Central Hospital (QECH) run by the College of Medicine; we will be able to capture clinical information about particularly serious burns using the Wellcome Trust funded QECH electronic patient tracking system (SPINE).

Household air pollution, personal exposure and concordance: Household air pollution (PM2.5, carbon monoxide) and personal exposure (randomly selected child under age of 4½: carbon monoxide, carboxyhaemoglobin; randomly selected adult member of household: as for children plus black carbon and PM2.5) will be measured in a random sample of up to 2000 households across the CAPS trial sites using previously described methodology (17,18). Specific detail including quality control and quality assurance processes will be set out in Standard Operating Procedures. Up to 48 hours of continuous indoor air quality monitoring will be conducted every 6 months to ensure we have a series of repeated measures from each monitoring episode. Similar methodology will be applied for the personal exposure assessments aspect except that the monitoring devices will be worn on the person and in addition, black carbon exposure and carboxyhaemoglobin will be assessed.

Utilisation of the advanced cookstove will be assessed using University California Berkley Stove Use Monitors (coin-sized heat detecting and recording devices that can be attached to the stoves) in 10% of trial households randomly selected from the intervention trial arm.

Taken together these measurements will allow us to determine if the substantial reductions in household air pollution levels observed from our preliminary work are also seen during the trial and how these relate to stove use and they will inform exposure-response relationship analyses.

Case Report Forms (CRF): Each child and adult included in the trial will have their own CRF that will identify the child via their Household Trial Number, Participant Trial Number, initials and date of birth. An electronic CRF will be used to make the large number of CRFs manageable and provide real-time data entry, internal validity and consistency checks. CRFs will be treated as confidential documents and held and backed up onto two secure servers.

Training clusters

At each site one additional (intervention) cluster will be included to provide an opportunity for the trial protocol to be implemented outside of the context of the main trial for training purposes, to ensure any local challenges are overcome, and that sufficient experience is gained in study methodology including the use of the electronic CRFs, using the cookstoves to maximize reductions in air pollution exposures attaining proficiency in air pollution monitoring. Twenty households will be included in the training clusters where all aspects of the full trial protocol will be implemented. Data collected from these clusters will not be included in the main trial analyses.

POST-RECRUITMENT RETENTION STRATEGIES

Potential problems with compliance

The transition from cooking over an open fire to using an advanced cookstove represents a large change in an activity that usually takes up a considerable part of the day, can be part of the social fabric of the village and associated with particular beliefs and superstitions. Nevertheless, we found high levels of cookstove adoption in our exploratory RCT in Ntcheu and in an acceptability study in Lesotho. With careful community engagement, support from community leaders and training in the use of the stove, initial innovation adoption is therefore likely to be successful. We expect that the advantages of the advanced cookstove in terms of reduced time needed for cooking, fuel consumption, smoke emissions and improved safety will help maintain high levels of use. The RESPIRE study helped to sustain high levels of compliance by providing a maintenance and repair service for the Plancha stove (15). We will do the same in this study. We will also assess compliance with the intervention through self-reporting and by Stove Use Monitors in 10% of intervention households. Compliance with the protocol and SOPs by field staff will be maximised through training events to include GCP training, and periodic quality control audits.

Likely rate of loss to follow-up

We will work to minimise loss to follow-up through active community engagement, responding promptly to trial-related difficulties, repairing and replacing stoves as needed and providing additional benefits to the participating villages (e.g. mobile phone access).

SAFETY MONITORING AND ADVERSE EFFECTS

Potential risks to the safety of the trial participants

Trial households will be recruited from populations living in often poor conditions in Malawi who live with relatively high day-to-day risks. The open fire that control households will continue to use is one contributor to these risks. The advanced cookstove is likely to be safer than the open fire since it contains the fire in a stable construction with outside surfaces that are cool to touch during use. All participating villages will benefit from a mobile phone with airtime and guaranteed availability of antibiotics for pneumonia treatment. Overall we expect participation in the trial in either the intervention or control group will reduce risks to participants.

Risk assessment

See appendix A for full risk assessment.

Data and safety monitoring

See Trial management section.

Adverse event reporting requirements

An adverse event (AE) is any unfavorable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study. A Serious Adverse Event (SAE) is an adverse event following the intervention that results in a) death, b) a life-threatening adverse event, c) hospitalization or prolongation of an existing hospitalization, d) disability or incapacity, e) congenital anomaly in the offspring of a participant.

The advanced cookstove intervention we will be using in this trial is a non-medical intervention and is not known to increase the risk of any adverse event. It is a particularly low-risk intervention that offers potential safety benefits (e.g. reduced risk of burns and fires). Nevertheless, we will collect data about adverse events. Data about AEs that are not serious will be collected at the routine three monthly field visits. Study participants will be asked to report SAEs immediately to the trial coordinating centre. The trial coordinating centre will collect details about the SAE using a proforma in accordance with a specific SOP. This information will then be passed immediately to Kevin Mortimer and Stephen Gordon who will conduct a causality assessment (not related/improbable, possible, probable, definite), assess seriousness and expectedness, take any appropriate medical action and inform COMREC and LSTM REC of any events deemed related to the trial intervention within 7 days of knowledge of the event. All other SAEs will be reported as part of an annual report to COMREC and LSTM REC. All SAEs will be followed to resolution.

DATA COLLECTION AND MANAGEMENT

This is described in the section on outcome assessments. An electronic data collection and management system will be used with in-built consistency, range and logic tests to maximize quality. The data collection tools will be GPS enabled allowing us to map the location of data collection episodes using Google Earth Pro. This will facilitate internal quality control checks and independent monitoring visits.

Progress and final reports
Progress reports will be sent annually with a final report at the end of the trial to the MRC, endorsed by the TSC. This will be submitted using the template in Appendix 3 of the MRC GCP guidelines (http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416).

SAMPLE SIZE

The sample size has undergone much consideration as this project has developed as explained and justified below together with our final sample size plan:

Original sample size assumptions

Following feedback from the JGHT Panel in December relating to our outline proposal we substantially increased the sample size to a) account for a change in design to village-level cluster randomization, b) reflect the effect size seen in the RESPIRE trial of a cookstove intervention on severe pneumonias (15) and c) use the latest available estimates of a health centre IMCI pneumonia diagnosis rate of 9 per 100 child-years from Karonga, Malawi.

In our full application we considered the potential impact of the introduction of pneumococcal vaccination on baseline pneumonia rates and took into account informed estimates suggesting around a 20% reduction in pneumonia rates could be expected in the Malawi-specific context (Neil French personal communication). Trials of the 9-valent pneumococcal vaccine in Soweto (19) and The Gambia (20) found a 17% (95% CI 4 to 28) and 37% (95% CI 27 to 45) vaccine efficacy on first episodes of radiologically-confirmed pneumonia in children respectively. There was higher vaccine efficacy on pneumococcus-specific disease in both trials but it is the overall impact on all-cause pneumonia that is most relevant for our trial. The 2009 Cochrane review of pneumococcal conjugate vaccines on invasive pneumococcal disease and X-ray defined pneumonia in young children pooled data from 11 publications and found the vaccine efficacy on WHO X-ray defined pneumonia was 27% (95% CI 15 to 36) and clinical pneumonia was 6% (95% CI 2 to 9) (21). In our original power calculation we allowed for a greater than expected impact of pneumococcal vaccination –a 45% reduction in pneumonias – to allow for unpredictable factors such as herd protection effects from nationwide vaccination. We therefore used the conservative assumption that only 5% of control group children will develop pneumonia of sufficient severity to require treatment at a health centre every year.

The effect size included in the original power calculation was a 20% reduction in pneumonia risk that approximated the reduction in physician-diagnosed pneumonia seen in RESPIRE (RR 0.84 or 0.78 after multiple imputation). Importantly we powered the trial to detect a smaller effect size than was seen in RESPIRE on severe pneumonias (RR 0.67). We used a conservative between-cluster coefficient of variation of 0.1. Furthermore the intervention we plan to use is an advanced cookstove that reduces smoke emissions and exposures by 80 to 90% while the *plancha* stove used in RESPIRE just vented emissions to the outdoor environment; there is therefore greater potential for impact with the advanced cookstove than was seen with the *plancha*.

Based on these various considerations we originally proposed a sample of 59 villages per group each with an average of 77 children (allowing for 10% loss to follow up from the average of 85 children per village) followed for an average of 1.7 years (affected by age of child at enrolment) and this sample size provided 80% power to detect a 20% reduction in the risk of pneumonia in the intervention group from 5% to 4% per annum and 90% power to detect a reduction to 3.8% (α=0.05). With 118 villages in total each with an average of 85 children per village, and 1.7 years average follow up this provided a *potential* total of just over 17,000 child years of follow up.

Final sample size

The sample size has been re-considered in the light of improved data now available from the currently planned CAPS sites in Chikhwawa and Karonga. Some of the assumptions underpinning the sample size calculations have also been re-considered.
The total number of children under the age of 5 years in Chikhwawa was estimated as being 5,027 in 2008. It is considered reasonable to assume that this number has now increased to approximately 5,600. There are 50 villages (clusters) in this district, giving an average number of children per cluster of 112.

The total number of children under the age of 5 years in Karonga was estimated recently as being 4,750. It is considered reasonable to assume that this number has increased to approximately 5,000. There are 278 villages (clusters) of 20-30 households in this district, giving an average number of children per cluster of 18.

This disparity in the average cluster size between the two study districts has implications for the power of the study. A paper by Eldridge, Ashby and Kerry (22) found that variation in cluster size reduces the statistical power of a cluster randomised trial - and that this effect increases as the variation in cluster size increases.

As the clusters in Karonga are relatively small, they can be combined to form larger clusters. To do so would appear to be counter-intuitive as cluster randomised trials work best with a large number of small clusters. However, this has to be weighed against the negative impact of having a large range of different cluster sizes. A compromise is needed between these two conflicting influences on the statistical power of this study.

The sample size calculations were re-worked extensively to identify a "best" compromise. In this context, "best" was defined as creating sufficient clusters to produce a feasible design structure (manageable number of clusters to be randomised) and to provide acceptable statistical power.

The compromise recommended is to collapse the current 278 clusters in Karonga to just 100 clusters. Combined with Chikhwawa this will provide a total of 150 clusters (75 clusters per intervention group). The total number of children in these clusters will be approximately 10,600. The average number of children per cluster will now be 70.7.

Assuming that actual cluster sizes range between 50 and 150 (a conservative estimate), the coefficient of variation in cluster size would be in the region of 30 - 35%. In which case, the paper by Eldridge, Ashby and Kerry recommends that the intra-cluster correlation (ICC) value assumed for the sample size calculations be increased by 20%.

The outcome measure for the CAPS study is the number of pneumonia cases in children under the age of 5 years recorded in each cluster over the two years of the study period. No loss to follow-up is now assumed in the sample size calculation, as the eligible number of children in an individual cluster can reasonably assumed to be constant. For each child who reaches their 5th birthday and hence becomes ineligible for the study, they will be replaced by (at least) one newborn child.

For the same reason, the number of child-years of follow-up in each cluster will be the number of children in the cluster at the start of the study period multiplied by two.

As previously, a conservative value of 0.1 has been assumed for the ICC (intra-cluster correlation). In line with the recommendation of Eldridge, Ashby and Kerry, this was increased by 20% to 0.12 for the sample size calculation.

A total of 150 clusters containing a total of 10,600 eligible children randomised in equal numbers to the two intervention groups will provide, over the whole study period, 21,200 years of follow-up and 90.3% power to detect a reduction in the (annual) risk of pneumonia from 5% in the control group to 4% in the intervention group (proportionally, a 20% reduction in risk), assuming an effective ICC value of 0.10 and a coefficient of variation in cluster size of 30-35%.

The same sample size will provide 80.4% power to detect a reduction in the (annual) risk of pneumonia from 5% in the control group to 4.125% in the intervention group (proportionally, a 17.5% reduction in risk), under the same assumptions.

Additional justification for sample size for air pollution exposure and lung function sub studies

Incidence-exposure analyses (children)
2000 children will be included in the incidence-exposure study and followed up until the end of the CAPS study period, giving an expected total of 2000*2.0= 4000 years of follow-up ("exposure"). Based on the work of Fullerton et al (6), it will be assumed that the mean levels of CO in children will be 16.31 (22.77) ppm. The anticipated annual pneumonia incidence rate averaged across the trial arms is 4.5%, which corresponds to an expected incidence rate of 7.53% per child. Assuming a Poisson model, the expected total number of pneumonia episodes is 150 – but as 5 children are predicted by this model to have more than one episode, the expected number of children who will experience at least one pneumonia episode will be 145. On a simple comparison of the 145 children who will experience pneumonia against the 1855 who will not, this study will have 90% power to detect a mean difference of 6.53 (40%) ppm or greater in mean CO levels between these two groups. If it is necessary to match each child who experiences pneumonia with just one child who does not on one or more confounding factors, the minimum detectable difference between the two groups will be 8.92 (55%) ppm.

Respiratory symptoms and lung function analyses (adults)
a) Baseline spirometry measurements will be recorded for the 2000 adults aged 18 and above recruited into this sub study (replicating the sample size taken for the BHS and BOLD study currently ongoing in the urban setting of Chilomoni ward) along with relevant demographic/clinical characteristics considered to potentially influence the development of chronic respiratory disease. Participants will be stratified into two age groups: 18-39 years and 40 years or above. If 500 males and 500 females (total 1000 individuals) fall into each age group, an estimate of obstructive lung disease prevalence in each gender / age stratum will be obtained with a precision (95% CI) of ±2.6 to ±3.8% (assuming a prevalence of 10 to 25%). Allowing for unequal age and gender distributions, refusals and inability to provide spirometry measurements of acceptable quality, a sample of just 300 participants in any one gender / age stratum will provide an estimate of obstructive lung disease prevalence in this stratum with a precision (95% CI) of ±3.3 to ±5.0% (again assuming a prevalence of 10 to 25%) [this minimal sample size is informed by the BOLD protocol].
b) The same 2000 adults will then be followed with repeated spirometry measurements for two years (the full duration of inclusion in CAPS). Assuming an ICC of up to 0.25 for possible clustering effects within villages, this study will have 90% power to detect a correlation between CO/particulate matter exposure and change in FEV1 level of 0.102 (or greater) in both age groups combined and 0.144 (or greater) in each age group separately.

ANALYSIS

Statistical analyses

All primary analyses will use intention to treat principles; secondary per protocol analyses will also be done. Generalised estimating equation modeling methods will be used to evaluate the primary response variable (occurrence of pneumonia episodes in children aged <5 years during study period), adjusting for clustering effects within villages; time to each event will be analysed using (multiple event) Cox regression methods, while number of events per child will be analysed using Poisson, negative binomial regression or logistic regression methods as appropriate. Terms will be included in these models for treatment arm, cluster (village) and important confounders and covariates (*e.g.* baseline characteristics) considered *a priori* to strongly influence outcome.

Incidence-exposure analyses (children)

Initially, the mean CO levels of those children who did and who did not experience any pneumonia episodes will be compared using linear regression models. The association between personal exposure to CO and actual number of pneumonia episodes will then be assessed using Poisson regression analyses with (logarithm of) time of follow-up ("exposure") as an offset; exposure response curves will be constructed for personal exposure to CO against pneumonia episodes. Finally, if sufficient pneumonia episodes are observed, Cox regression models will be used to evaluate time between episodes, allowing for multiple episodes per child. All analyses will include appropriate adjustments for important factors and covariates.

Respiratory symptoms and lung function analyses (adults)

(a) The BOLD data will be analysed in accordance with the BOLD protocol (www.boldstudy.org). Response rates, the characteristics of the study participants, and COPD prevalence estimates will be reported with 95% CIs. A logistic regression model will be used to explore factors associated with COPD prevalence.

(b) Longitudinal spirometry data will be analysed using the using the linear random-intercept models proposed by Romieu et al, with adjustment for potential confounders including age, gender, height, location, socioeconomic status, smoking status, passive tobacco smoke exposure and HIV status where known (15). The extent to which personal exposures to CO and particulate matter explains the change in FEV1 over time will be explored.

All analyses will be performed using the Stata v13 statistical software package.

A detailed statistical analysis plan will be presented to and approved by the Data Monitoring Committee (DMC) prior to trial commencement.

Interim analysis plan

One blinded interim analysis will be carried out by the independent statistician on the DMC halfway through the follow-up period. The aims of this analysis will be to determine a) whether there are grounds to stop the trial for safety or efficacy (the Peto-Haybittle rule ($p<0.001$) will be used to guide stopping for efficacy) and b) whether the incidence of pneumonia episodes being observed is compatible with the assumptions made in the sample size calculations detailed above. If there is concern that the observed overall event rate is very different from that anticipated, a blinded revision of the total sample size estimate will be done using the methods advocated by Gould (23,24); this simple formula is based on the predicted and current (*i.e.* at time of the interim analysis) proportion of participants overall who have experienced a pneumonia event, and has a considerable advantage in that it "preserve[s] the power [of the study] and [does] not affect the type I error rate materially" (25). If subsequently there is concern that the observed overall event rate is much higher than anticipated and hence there might be concerns over safety, a blinded comparison of the event rates in the two study groups will be carried out using the methods advocated by Wassmer et al (25) and by Posch and Bauer (26).

Planned subgroup analyses
We will estimate benefit in relation to reductions in household air pollution, personal exposure and stove use in the subgroups for which we have those data.

Methods for protecting against sources of bias
We will use cluster randomisation, allocation concealment and a control group. An open design is unavoidable given the intervention. To minimise the risk of bias from a non-blinded study we will a) provide specific training to fieldworkers to ensure participants are treated in the same way irrespective of trial arm; b) schedule the same frequency (3-monthly) of field visits to intervention and control villages to repair/replace cookstoves and mobile phones if necessary, troubleshoot trial-related problems; c) collect primary outcome data in the same way for intervention and control villages; d) provide training to local healthcare workers about how to make an IMCI diagnosis of pneumonia, the importance of carrying out assessments and treatment based on clinical need and without enquiring about trial allocation to achieve blinded assessment of the primary outcome e) submit the evidence upon which all pneumonia diagnoses are made for review by a fully blinded Independent Endpoint Review Committee.

ETHICAL ASPECTS

We will request ethical review of the trial protocol and other documents by the College of Medicine Research Ethics Committee (COMREC) in Malawi and LSTM Research Ethics Committee (REC) in the UK. The trial will not commence until we have ethical approval from both committees.

Participant information and consent

Following community sensitisation events and distribution of written information sheets in English, Chichewa or Chitumbuka, consent to conduct the study in the cluster will be obtained from a village-level representative (see appendix B)

All participants will be given a written information sheet using the University of Malawi College of Medicine template (see appendix B) to read in English, Chichewa or Chitumbuka. This will be read out to all participants to facilitate discussion and ensure that inability to read is not an obstacle to participation.

Written informed consent will be obtained from all participants (see appendix B). A mark witnessed by someone independent to the study will be accepted where participants are unable to sign.

The informed consent process will emphasise that participation in the trial is voluntary, that consent to participation can be withdrawn at any time, without giving a reason and without this affecting their current or future medical care or benefits to which the participant is entitled. No trial-related interventions will be conducted prior to obtaining informed consent.

Participants will be informed about any relevant information about the intervention that becomes available during the course of the trial. Where necessary, the participant information sheet and consent form will be amended and, following ethical approval, renewed consent to continue participation requested.

TRIAL MANAGEMENT

Trial protocol review and registration

The protocol will be submitted for review by The Lancet and the final approved protocol will be registered with Current Controlled Trials Ltd (http://www.controlled-trials.com/) and published in an open access format.

Arrangements for day-to-day management

A full time on-site qualified and experienced Clinical Trials Manager (CTM) will be appointed and have responsibility for day-to-day management issues, supervision of field workers and data manager, protocol compliance, security of the randomisation process, recruitment, data management, problem identification and resolution, distribution and maintenance of trial materials, budget control and production of annual progress reports. The CTM will be supported by a middle-grade clinician (Malawian graduate), Kevin Mortimer (KM) and Stephen B Gordon (SBG).

A Trial Management Group (TMG) led by the CTM will be established to manage the trial on a day-to-day basis and will include the middle grade clinician, KM or SBG and the senior fieldworker(s). The TMG will meet at least monthly and will monitor trial conduct, progress (including recruitment, withdrawals and losses to follow-up), adherence to the protocol and SOPs, CRF completion, accuracy and completeness of data collection, data validity and where necessary act to safeguard trial participants and quality standards. The TMG will receive logistic and infrastructural clinical trials support from MLW and The Wellcome Trust Tropical Centre in Liverpool.

Responsibilities of the co-investigators

The investigators are a collaborative group of international experts in household air pollution, public health, clinical trial design and implementation, biostatistics, health economics, qualitative research and improved cookstove development and dissemination. We will be drawing on valuable experience gained from conducting the RESPIRE trial in Guatemala; wide ranging knowledge, skills and expertise from academic groups at LSTM, the Universities of Liverpool, London, California and Malawi; considerable local knowledge and ability to implement research and aid programs in challenging environments. All applicants have been involved in the trial design. Specific responsibilities during the implementation, analysis and dissemination phases will be: **Stephen B Gordon** (SBG) and **Kevin Mortimer** (KM) will share Principal Investigator responsibilities and, together with a dedicated local clinical trials clinician, will provide full time on the ground clinician oversight and support for the CTM. SBG has lived and worked in Africa for 15 years and has particular expertise in field, clinical and laboratory research on the adverse effects of biomass smoke exposure on health and alveolar macrophage function and pneumococcal disease. KM has run clinical studies in respiratory medicine in the UK, conducted pilot work in Ntcheu, and has experience of working in Queen Elizabeth Hospital in Blantyre. He will commit 50% WTE to trial implementation, management and oversight activities with flexibility to work from the UK or Malawi as necessary.**Moffat Nyirenda**, Associate Director of MLW, will lead on high-level trial implementation activities and ensuring the trial delivers benefits in line with MLW research strategy. **Anja Terlouw** leads and conducts epidemiological research at the MLW Chikhwawa field site and brings particular local knowledge, skills and expertise that will help the successful implementation of the trial at this site and ensure the trial provides added value to research activities there. **Jonathan Grigg** (JG) is an experienced paediatrician with expertise in the management of childhood pneumonia and research expertise in air pollution exposure assessments that includes fieldwork in Africa involving induced sputum macrophages as exposure biomarkers. He will lead a working group on household air pollution and personal exposure to deliver this aspect of the proposal. **Nigel Bruce** (NGB), **John Balmes** (JB) and **Dan Pope** (DP) bring wide-ranging benefits to the trial through their experience of conducting the RESPIRE trial in Guatemala. NGB and JB have played key roles in the GACC Health Working Group (NGB co-chair), the World Health Organisation Department of Public Health and Environment (NGB) and other international organisations with particular strategic relevance to disseminating the results of this trial at high level meetings and ensuring the findings inform policy and decision makers. NGB

and JB will lead on these activities. JG and JB will establish the Independent Endpoint Review Committee. DP will lead on updating our systematic review to include the trial findings. **Brian Faragher** has extensive experience as the statistician for numerous large trials in Africa and elsewhere. He will be the statistician for this trial, oversee the establishment of the DMC and use opportunities provided by this trial to build Malawi-based capacity in statistics. **Lesong Conteh** brings expertise in health economics and health system research in sub Saharan Africa and will lead this on this aspect of the trial. **Margaret Matinga** will conduct the qualitative work and is particularly well placed to do this as a Chichewa speaking Malawian woman (highly relevant for the interviews with female villagers) with a PhD in energy anthropology.

Responsibilities of the staff employed on the grant
The CTM will have the responsibilities set out in above. A dedicated local clinical trial clinician will, together with SBG and KM, provide full time accessible clinician oversight and support for the CTM. The fieldworkers will undertake community engagement and support activities, baseline mapping of villages, recruitment, implementation of randomization schedule, collection of baseline and follow up data and data entry into electronic CRF. The data manager will train and support fieldworkers in the use of the electronic CRF, manage and maintain the data collection and management systems used, generate summary datasets when needed for the DMC, produce a full cleaned dataset at the end of the data collection period for the trial statistician. We have included a contribution to LSTM/MLW administrative, governance and finance support.

Research governance arrangements
Trial oversight committees (TMG, TSC and DMC) will be established. The trial will be run according to the MRC Guidelines for Good Clinical Practice in Trials. MLW/LSTM will perform an initial start up and then annual GCP compliance visits to ensure and document complete compliance. All trial staff and investigators will protect the rights of the trial's participants to privacy and informed consent. Internal quality control monitoring will be conducted 3-monthly to ensure understanding of protocol and SOPs, protocol and GCP compliance, conduct source document (health passports) verification and confirm all participating households have given written informed consent. Participation in the trial involves low risk interventions and procedures that are not expected to increase the risk of Serious Adverse Events (SAE) above the normal baseline for poor people in Malawi. All SAEs will be reported to the TSC and DMC and via onward reports to COMREC and LSTM REC. Trial participants and trial staff will be covered by LSTM indemnity and insurance. The Principal Investigators will maintain all records and documents regarding the conduct of the study and retain these for at least 7 years or for longer if required. The Trial Master File and trial documents shall be finally archived at secure archive facilities at LSTM or MLW.

Data Monitoring Committee
The DMC will be independent of the investigators, sponsor and funder with an independent chair (Professor Stephen T Holgate CBE) and independent statistical support. The DMC will meet initially before the trial commences to review the protocol and agree Terms of Reference (TOR) and then once more when half the potential follow-up experience has accrued to review indications to stop the trial for efficacy, safety or futility. The DMC will report to the TSC.

Trial Steering Committee
A TSC will be established to provide overall supervision of the trial and ensure the trial is delivered in accordance with the MRC's Guidelines for Good Clinical Practice.The TSC will have an independent chair (Professor Anne E Tattersfield OBE), include 2 other independent members (independent membership being the majority), SBG and KM. Representatives of the Trial Funder and Sponsor will be invited in advance to all TSC meetings, receive papers and minutes. The TSC will initially meet face-to-face prior to trial initiation to agree the trial protocol and TOR (aligned with MRC GCP guidelines (http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416) and then convene at least annually thereafter through conference calls and 1 further face-to-face meeting if needed. KM in association with the chair will take responsibility for calling and organising TSC meetings.

ECONOMIC EVALUATION AND HEALTH SERVICE RESEARCH

An economic evaluation will be conducted to identify the incremental costs and benefits to health care providers and households associated with using cookstoves compared to open fires. Cost effectiveness ratios will be presented from 3 perspectives: i) intervention costs alone; ii) potential costs/savings to health providers (MoH); iii) potential societal costs/savings.

Costs to healthcare providers and households associated with cookstove use will be collected as part of routine trial data collection, with supplementary cost and resource use data collected where necessary. In addition, the economic costs to providers of treating 150 inpatient and 150 outpatient visits in which pneumonia is the primary diagnosis will be calculated from a representative subsample of health facilities.

A standardised costing template will be used in all the sites to record resource use associated with personnel, drugs, materials and supplies, equipment, transport, utilities and buildings. A standard ingredients approach will be used which involves costing the quantity used and the value of each unit of input needed to provide an inpatient or outpatient visit. Effects will be based on trial outcomes. Specifically, the cost per episode of childhood pneumonia averted and Disability Adjusted Life Year (DALY) saved will be calculated.

A threshold analysis will explore at which point the intervention is no longer cost effective at changing epidemiological and economic parameters. Probabilistic sensitivity analysis will be conducted to investigate the uncertainty surrounding model assumptions and the key drivers of outcomes.

Qualitative analyses will explore quality of life attributes, attitudes, beliefs and behaviours that may be relevant for scale-up of the intervention. Specifically we will identify opportunities for change, motivations and barriers to change and skills required to support the various change (adoption) stages, under themes of: understanding cultural values of the fireplace; gender dynamics in technology adoption; food preparation and taste; knowledge and cultural interpretations of respiratory infections; actual and perceived affordability; functional and desirability (*e.g.* convenience, aesthetics and prestige) perceptions.

CONSUMER INVOLVEMENT

Local health service involvement

We will work with local health service leaders and providers to ensure this trial does not have local health service cost implications. Assessment of the primary and secondary health outcomes for the trial will not demand additional work beyond good standard practice *i.e.* use of the IMCI pneumonia protocol for patient assessment and documentation of the diagnosis and treatment in the patient's health passport. To help achieve high standards of clinical assessment and documentation we will provide training in use of the IMCI pneumonia assessment protocol for paediatric healthcare workers at 6 monthly training events (which will include additional educational activities *e.g.* case discussions) at local health facilities. We will use these opportunities to raise and maintain awareness of the trial, the importance of fully documenting pneumonia diagnoses and severity assessment in patients' health passports avoiding enquiry about trial arm allocation.

Planned ongoing involvement of community groups in the trial

We plan ongoing involvement of trial participants, other community members and community leaders through trial set-up, implementation and dissemination phases. Specifically there will be community engagement meetings led by field workers before trial initiation to obtain input into trial implementation plans and wording of participant information and consent forms, there will be meetings every 3 months during implementation with an open agenda and when the study results are available these will be presented and discussed at community meetings in all included villages.

REPORTING, DISSEMINATION AND NOTIFICATION OF RESULTS

How the results of this trial will be used

High quality clinical trial evidence about the health and economic impacts seen when households adopt advanced cookstove technologies is needed to inform policy and decision makers across commercial, health, development and community sectors at local, regional and international levels. The results of this trial will be relevant to local policy makers in Malawi who will have new efficacy, economic, acceptability and uptake data to guide decisions about funding advanced cookstove programmes for improving child health; to regional commercial, non-governmental (NGO) and governmental organisations in sub Saharan Africa making and distributing cookstove solutions with uncertain health benefits; and to international (*e.g.* WHO) decision and policy makers by contributing new evidence about health, exposure-response and economic impacts of an advanced cookstove intervention of broadly generalisable relevance to areas of the world where biomass fuel use is common. We have established local (*e.g.* community leaders), regional (*e.g.* commercial, NGO, MoH) and international (*e.g.* WHO and GACC) links that will help us disseminate the trial findings effectively at all levels to a wide range of stakeholders, policy and decision makers.

How the results of the trial will be generalisable beyond the immediate research setting of the trial

The key question this trial will answer is whether an intervention that substantially reduces biomass smoke exposure compared to open fires can prevent pneumonia in children under the age of 5 living in poverty in a developing country. There is good evidence from the RESPIRE trial that the major determinant of health benefits from a cookstove intervention is the extent of biomass smoke exposure reduction rather than the intervention *per se* (15). Although we will be studying a specific stove our findings will be applicable to biomass smoke exposure reduction interventions more generally given that smoke exposure reduction is the mechanism of beneficial effects. Our findings will also be generalisable beyond Malawi; should we see a reduction in childhood pneumonia from an effective biomass smoke exposure reduction intervention the implications of this finding will be relevant to people throughout the developing world who cook over open fires.

Links which are likely to improve the likelihood of successful implementation of results of the trial.

We are part of an established network of local, national and international links that will facilitate the successful wide dissemination and implementation of the results of the trial. This network includes grass root community representatives, NGOs, local healthcare workers, ACE, ARC, Malawi MoH, COM, MLW, WHO and GACC Health Working Group.

Publication policy

The trial findings will be presented at international conferences and published in peer-reviewed journals with open access.

Approach for managing, preserving and sharing data generated

In line with The Wellcome Trust Data Sharing Policy and Guidance and The MRC Data Sharing Policy we will make our full research database publically available once we have published our findings. The only limits to data sharing will be to safeguard research participants' confidentiality. We will provide a link from the LSTM website to study-related resources including the protocol, participant information sheets, standard operating procedures, publications and the database. These resources will be maintained in this low cost format (covered by budget) for the long-term.

Disseminating results to the public

We will communicate the findings of our work to participating villages in Malawi through a series of community engagement meetings. We will present our work through other community engagement activities held by the College of Medicine, MLW and LSTM in Malawi and the UK. We will actively participate in DFID, MRC and Wellcome Trust public engagement opportunities available to us.

Intellectual property/commercial exploitation

We will follow customary academic practice and the Liverpool School of Tropical Medicine's (LSTM) standard approach to managing project related intellectual property which is that ownership will reside with the institution that generates the same. LSTM has extensive experience in managing similar projects such as the EU funded AntiMal project www.lstmliverpool.ac.uk/research/major-research-projects/antimal/) and the BMGF funded Innovative Vector Control Consortium (www.lstmliverpool.ac.uk/research/major-research-projects/ivcc/) and has clear objectives to make the outcomes of its research available, as soon as is practicable, for the benefit of the poor in developing countries. Wherever possible, outcomes from the trial will be published and made available on an open access basis and any potential exploitation of the results will be managed by LSTM.

Although the trial will use a specific commercially-produced cookstove as the means of achieving the intervention, the key intervention of interest is the reduction in biomass smoke exposure rather than the cookstove *per se*. Positive outcomes from this trial could be commercially exploited by manufacturers of other advanced cookstoves that substantially reduce smoke exposure. This could stimulate investment in further innovation and improvement in affordable, acceptable and accessible cookstove technologies and a thriving market in clean cookstoves. These beneficial effects would therefore fully align with the objectives of the United Nations Foundation-sponsored Global Alliance for Clean Cookstoves, which is "a public private partnership that seeks to save lives, improve livelihoods, empower women and combat climate change by creating a thriving global marker for clean and efficient household cooking solutions" (www.cleancookstoves.org/). None of the potentially commercially exploitable results will be based on tissues or samples derived from participants.

PATHWAYS TO IMPACT

We are part of an established effective network of local, national and international partners (BREATHE-Africa consortium) committed to improving health and reducing poverty in sub Saharan Africa and other less developed areas of the world. This trial will deliver new high quality evidence regarding health, societal and economic effects seen when households adopt advanced cookstove technologies. There are pathways to beneficial impacts in the locale of the study, in the sub Saharan Africa region and internationally:

In the locale of the study, we will achieve economic, societal and environmental impact by engagement with research participants and staff, predominantly within the *modus operandi* of the study.
At regional level we will achieve health policy and commercial impact during the life of the grant by planned engagement with Malawi Ministry of Health and NGO partners.
At international level, the results of the trial will inform international policy through national governments, the Health Working Group of the Global Alliance for Clean Cookstoves [Prof Stephen B Gordon (SBG) is a member and Prof Nigel Bruce (NGB) is co-Chair] and WHO (NGB seconded).

Impact in the locale of the study

Economic Impact: This study will take place among very impoverished people. All participating households will receive benefits from taking part including two efficient-burning cookstoves either at the beginning or end of the trial. Reduced fuel consumption will translate to less time spent gathering wood and the potential for alternative profitable activity. We will maximise the economic impact of these interventions by working with carbon trading partners in Malawi to secure carbon credits for villages beyond the trial implementation phase. We have experience of community engagement and carbon trading while measuring domestic exposures and in a pilot stove intervention evaluation.

Societal: The study will ask for changed cooking behaviour and will have a high local profile. Discussion around health, pollution, reduced burns risk and diet offer the opportunity for diverse educational messages including diet, access to health care (reinforced by phone and antibiotic availability) and the health effects of cooking smoke. The telephone and regular visits provided to each village will increase communication and access generally. Margaret Matinga has particular expertise in this area in both South Africa and Malawi. We will conduct a series of village-level events ("msonkhano" is the accepted means of community announcement and discussion) to maximize the local benefits of the trial.

Environmental: The study will directly reduce the amount of wood burned and will therefore reduce environmental destruction. Extensive work by Concern Universal has indicated that cookstove uptake is highest in villages with limited wood availability.

Local staff: Local people will be employed on the project and other local people involved indirectly. The training and experience gained (including specific training in clinical trial design, conduct and analysis) will lead to improved work opportunities in the future, particularly in Non-Governmental Organisation (NGO)-funded poverty alleviation programmes. Further, there will be immediate financial benefits for individuals receiving a salary and their families. In our previous studies (WT grant 2008, pilot study 2010) field workers in air monitoring or cookstove studies adopted altered cooking practice and health care seeking behaviour in their own homes.
These local impacts will all be achieved as a direct result of protocol implementation (including the Focus Group Discussions of the economic evaluation) and will be monitored by Dr Kevin Mortimer (KM).

Sub Saharan Africa Regional impact

Women and children living in poverty in developing countries
The primary outcome sought is a reduction in childhood pneumonia from an effective biomass smoke exposure reduction intervention. Secondary outcomes will include other health benefits, economic advantage, educational benefit and increased societal engagement with innovation. Increased awareness of the primary goal and the potential secondary benefits will be achieved by quality video presentation in a format similar to BBC News website articles targeted at the NGO and professional Malawian community. We will commission a video team in year 1 to film a piece which will describe the background, study questions and time-line of the study. This video will be used in website, face-to-face and webinar presentations to engage stakeholders. Experience in other sectors (solar power, wind power) indicates that urban-based, web-browsing professional Malawians are influential in their home village communities. Further, the Partnership for Clean Indoor Air (PCIA) of which we are members, has made increased use of webinar and web-based media to share experience among the energy sector NGO community. We have used video web-based media in the NIHR within the UK (SBG, Liverpool BRC) and SBG will deliver on this goal with help from Malawi Liverpool Wellcome Trust (MLW) and LSTM public engagement officers. We will maximize the dissemination and impact of trial findings regionally through full engagement with the press including press releases and media interviews and translation of research findings into regionally appropriate formats with lay summary information on accessible websites.

Public Sector
We have experience of outreach Continuing Medical Education (CME) activity in Malawi, both in the public sector and private sector. These have been welcomed in the past when operated from the MLW programme. KM and SBG will provide regular supportive training to local healthcare facilities to deliver CME at each centre. Material will include the use of the Integrated Management of Childhood Infection (IMCI) pneumonia assessment protocol as well as core medical topics.

Business/Industry
The Philips stove that has been chosen for this project will be keenly watched by the sector; stove production has been sponsored in the sub Saharan Africa region in anticipation of a sustainable production and sales pipeline. Our study data will set the standard required of less expensive stoves and these data will be released when available and in conjunction with the WHO Indoor Air Standards Committee (NGB, Chair).

Third Sector
NGOs implementing cookstove programmes require exposure-response data regarding the health effect of biomass smoke reduction strategies. We will deliver this impact by continued engagement with relevant NGOs and PCIA. We will attend the PCIA annual conference and offer a webinar with presentation of our data when available.

Higher Educational Institutions
The College of Medicine and MLW have a strong track record of successful public engagement programs to increase public awareness and understanding of science, economic and societal issues. We will engage fully with these activities that include public lectures, exhibitions, open days and conferences.

Impact on international policy
The trial findings have a clear pathway to impact on international policy through our established high-level involvement with policy and decision making organisations:

WHO Indoor Air Quality Standards: NGB chairs this advisory panel and will ensure that our data impact on future revisions of the standards due to be published in 2012.

Global Alliance for Clean Cookstoves Health Working Group (HWG): SBG (member) and NGB (Chair) serve on the HWG in order to advise research strategy to maximize health benefit in indoor air pollution initiatives. The HWG has been charged with advising Wellcome Trust, Gates, MRC, DFID, NIH and other major donors. The alliance is mobilising expertise to assess options for market development and innovative finance in partnership with governments, NGOs and private partners worldwide that will provide a framework for scaling up interventions based on outcomes of trials like this. Our trial maps directly onto research priorities identified by the HWG in 2011.

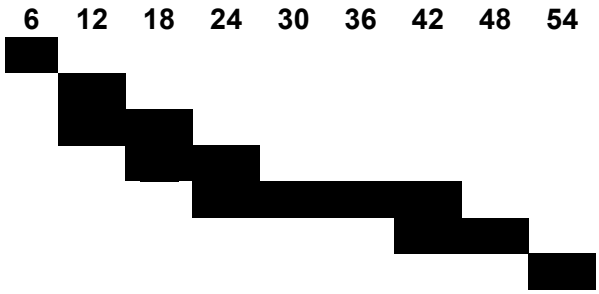
Carbon Finance Initiatives: Carbon credits offer a sustainable method of delivery for future cook stove initiatives. We will ensure that our project video and data reach Carbon Financing groups via NGOs in Malawi, PCIA, Global Alliance for Clean Cookstoves and WHO globally.

Measures of success of our impact activities

We will assess the success of our impact activities through qualitative evaluations conducted at village-level by Margaret Matinga, quarterly community engagement discussion forums, feedback questionnaires at project events, stakeholder (public sector, business, third sector and other) surveys and website statistics. Impact on international policy will be assessed using conference and publication citations linking our trial findings to policy and public health decisions.

SUMMARY TIMELINE

Task	Description
1	Ethical and other regulatory approvals
2	Staff recruitment
3	Practical trial set up activities
4	Mapping, recruitment and randomisation
5	Follow up and study completion
6	Data analysis
7	Report writing and dissemination activities



TRIAL FUNDING ARRANGEMENTS

Funders
DfID, Medical Research Council, Wellcome Trust

REQUIREMENTS AND JUSTIFICATION OF RESOURCES

Staff

A full time on-site qualified and experienced Clinical Trials Manager (CTM) will be appointed and have responsibility for day-to-day management issues, supervision of field workers and data manager, protocol compliance, security of the randomisation process, recruitment, data management, problem identification and resolution, distribution and maintenance of trial materials, budget control and production of annual progress reports. A dedicated local trial clinician will, together with Stephen Gordon (SBG) and Kevin Mortimer (KM), provide full time accessible clinician oversight and support for the CTM. A full time data manger is needed to train and support fieldworkers in the use of the electronic CRF, manage and maintain the data collection and management systems used, generate summary datasets when needed for the DMC, produce a full cleaned dataset at the end of the data collection period for the trial statistician. 15 fieldworkers will be needed to undertake community engagement and support activities, baseline mapping of villages, recruitment, implementation of randomisation schedule, collection of baseline and follow up data and data entry into electronic CRF. This includes some float for sickness, maternity leave and other possible threats to the availability of this body of staff critical for day-to-day trial implementation activities. A 50% WTE Malawian research assistant will conduct the health economics work under the supervision of Lesong Conteh. We have also included support for research governance (10% WTE) finance (10% WTE) and administration costs at LSTM (25% WTE) and MLW (100% WTE).

Staff – directly allocated posts

SBG and KM will share PI responsibilities with 5% and 50% WTE commitment respectively to trial implementation, management and oversight activities with flexibility to work from the UK or Malawi as necessary. Other Co-Is will dedicate up to 5% WTE to the project. Anja Terlouw will oversee trial implementation at the MLW Chikhwawa field site and ensure the trial brings added value to research activities there. Jonathan Grigg (JG) will lead a working group on household air pollution and personal exposure to deliver this aspect of the proposal. Moffat Nyirenda (MN), Nigel Bruce (NGB) and John Balmes (JB) will lead on trial strategy and high-level implementation activities. MN will ensure the trial delivers benefits in line with MLW research strategy. JG and JB will establish an Independent Endpoint Review Committee. Dan Pope (DP) will lead on updating our systematic review to include the trial findings. Brian Faragher will be the trial statistician, oversee the establishment of the DMC and use opportunities provided by this trial to build Malawi-based capacity in statistics. Lesong Conteh will lead on the health economic evaluation aspect of the trial. Margaret Matinga (MM) will conduct the qualitative work.

Travel and subsistence

We will make maximal use of telephone and web-based conferencing facilities to keep international travel and subsistence costs to a minimum. However a relatively high number of international trips will be essential to ensure sufficient training and support for Malawi-based trial staff, direct trial work and oversight. We have included funding for a total of 6 return trips from the UK to Malawi per year to cover trips by SBG and KM, 2 return trips over the course of the grant for LC for economic evaluation work, 2 trips for JG and a technician to provide training and follow up in household air pollution measurements, exposure and stove use monitoring and induced sputum processing and analysis. MM will make 2 return trips from South Africa to conduct the qualitative work. International flights and subsistence costs are included for 2 face-to-face TSC and DMC meetings. The LSTM/MLW clinical governance teams will incur some travel costs. We have also included and funding for a total of 6 individual international trips shared between co-investigators (including subsistence and conference fees) to enable us to disseminate our findings widely on the international stage.

Other directly incurred costs

Directly incurred costs in the UK are justified here. Most of these costs will be incurred in Malawi and are justified under ‘exceptions’.

We will register the trial with Current Controlled Trials Ltd and pay the fees associated with the LSTM REC review.
We have included the costs of convening a monthly teleconference between UK and Malawi-based staff and 3 annual TSC meetings.
Incidental costs additional to travel, subsistence and teleconferences incurred in convening the TSC and DMC meetings are included.
The Independent Endpoint Review Committee will require around 70 hours work for 3 consultant-level doctors.
An electronic CRF will be used and therefore development and support costs for this are included.
A UK trial insurance policy is required.

Impact
We have included the costs of 4 open access publication of our main trial findings, a trial website and associated data depository and Pathways To Impact video creation. Malawi-based impact activities are justified under 'exceptions'.

Other Directly Allocated Costs
N/A.

Research facilities (at Research organisations)
N/A.

Pooled and infrastructure technicians
N/A.

Exceptions
Our estimates of Malawi-based costs are based on our current experience of conducting community studies in Malawi including the ACTia trial in Chikhwawa.
We will pay the fees associated with the COMREC review.
Fieldworkers will need to make the following trips to each village: two mapping and community engagement visits by motorbike before randomisation, a visit by 4x4 to distribute the main consignment of stoves and 8 follow-up visits over two years using motorbikes. We will be required to pay a locally agreed standard monthly field allowance of £40 per fieldworker.
12000 cookstoves (allowing for 10% requiring replacement during the trial) will be purchased and shipped from Lesotho to Malawi. Our trial partner African Clean Energy has committed to making these stoves available to us at the lowest possible price. This commitment extends beyond the trial to up scaling of the intervention if indicated.
The battery that powers the fan in the cookstove requires charging intermittently and we have requested funds to cover these costs.
Each fieldworker and the trial clinician will need a smartphone for data collection during field visits and use for other tasks. The data manager, trial manager, research assistant and administrative assistance will also need a computer each. An external hard drive will be needed at each centre for data backup. A combination printer/scanner and consumables will provide for printing and scanning needs.
Each member of trial staff will need a mobile telephone and airtime credit to allow them to communicate effectively from different locations.
Funding has been included for all trial staff to receive GCP training and for 4 senior Malawian staff to do an online MSc in Clinical Trials (or similar) that will be relevant to the conduct of this trial and contribute to local capacity building.
Three annual GCP compliance visits by the MLW/LSTM governance teams have been included.
Local trial insurance cover is required.
There are infrastructure and support cost contributions for each research centre (including office space rental, utilities, internet and landline telephones).
Funding is requested for stationary and printing costs which will be minimised through the use of IT wherever practical.

All villages will be provided with a mobile phone with an airtime voucher that will be kept by a CAPS village representative.
A supply of antibiotics that reflects local prescribing practice for pneumonia will be provided to local health facilities if antibiotics are indicated following clinical assessment but otherwise unavailable.
We have included an emergency fund to allow us to assist with the transfer of sick children to hospital if necessary.
A new health passport will be provided to all children included in the trial, if needed. A sticker will be inserted in the front of each passport explaining that the patient is in a trial with a brief summary of the IMCI pneumonia assessment protocol and boxes to tick if the patient is diagnosed with pneumonia and if so whether this was severe or not. These measures are to facilitate high quality clinical assessments and documentation.
To help achieve high standards of clinical assessment and documentation we will provide training in use of the IMCI pneumonia assessment protocol for paediatric healthcare workers at local health facilities every 6 months. Although healthcare workers and the local health centers' will not be expected to do anything beyond good standard practice *i.e.* use of the IMCI pneumonia protocol for patient assessment and documentation of the diagnosis and treatment in the patient's health passport, the trial outcomes will be highly dependent on the quality of these assessments and their documentation. We therefore include some additional value for the healthcare workers and centers' by providing an allowance for attendance at the training sessions to include provision of a personal finger pulse oximeter which will be used for pneumonia severity assessments, additional locally tailored educational sessions during the training days and a contribution towards the medical equipment fund for each district hospital involved.
To conduct the household air pollution and exposure monitoring, stove use monitoring and induced sputum work, household air pollution monitors ($PM_{2.5}$, carbon monoxide), personal exposure monitors (black carbon, carbon monoxide, carboxyhaemoglobin), stove use monitors and associated software.
We have included funding for presentation events in Malawi and funding for a half day or evening event at each of the 150 included villages at which the trial findings will be presented in a locally tailored format with refreshments.

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Appendix A, B, C

Please contact us for more information

Conflicts of interest

The study investigators have no conflicts of interest to declare.