

UNIVERSITY OF CAPE TOWN

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Development of harmonised approaches for detecting and  
recording participant-reported antimalarial drug safety data: the  
Delphi process

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*submitted in partial fulfilment of the requirements for the degree*

MASTER OF PUBLIC HEALTH

in the

SCHOOL OF PUBLIC HEALTH AND FAMILY MEDICINE

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**PART 0: PREAMBLE**

## **DECLARATION**

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*Humba Makombe naMaokomavi*

## **ABSTRACT**

Eliciting adverse event (AE) and non-study medication reports from clinical research participants is integral for evaluating drug safety. However, using different methods to question participants yields inconsistent results, compromising the interpretation, comparison and pooling of data across studies. This is particularly important given the widespread use of antimalarials in vulnerable populations, and their increasing use in healthy but at-risk individuals as preventive treatment or to reduce malaria transmission.

Experienced, qualified antimalarial drug clinical researchers were invited to participate in a Delphi process, to facilitate consensus on what panellists consider to be optimal (relevant, important and feasible) methods, tools, and approaches for detecting participant-reported AE and non-study medication data in uncomplicated malaria treatment studies.

This Delphi built on a previous survey conducted among malaria clinical researchers about different elicitation methods they used. The findings thereof, and a summary of relevant literature, were presented to Delphi panellists in round one after which they were asked to suggest further questioning methods or approaches that they considered as important and feasible for asking participants (or their caregivers) about their health to collect adverse events, and use of non-study medications to collect previous or concomitant medication data.

In round two, the panellists were presented with the collated suggestions from round one to rate each type of question in terms of its relevance, importance and feasibility. Here, panellists would rate methods or approaches as either optimal or not optimal for inclusion in a 'menu' of harmonized or standard types of core questions to be used in a variety of uncomplicated antimalarial treatment studies.

In round three, panellists were presented with a summary of items which had achieved consensus in round two and, for items that had not achieved consensus they were asked whether or not they wished to change their response in view of the group's overall response.

Of the 72 invited, 25; 16 and 10 panellists responded to the first, second and third rounds of the Delphi process respectively. Overall, 68% of all questioning items presented for rating achieved consensus. When asking general questions about health, panellists agreed to include a question/concept about any change in health, taking care to ensure that such questions/concepts do not imply causality. Eighty-nine percent (39/44) of structured items about specific signs and symptoms, were rated as optimal. For non-study medications, a general question and most structured questioning items were considered an optimal approach. The use of mobile phones, patient diaries, rating scales as well as openly engaging with participants to discuss concerns were also considered optimal complementary data-elicitation tools.

This study succeeded in reaching consensus within a section of the antimalarial drug clinical research community about using a general question concept, and some structured questions for eliciting data about AEs and non-study medication reports. The findings suggest that one method of questioning may not be superior to another, or sufficient to fulfil its purpose on its own and that the use of a combination of methods may be optimal. As malaria clinical research is often conducted in children (and other vulnerable groups), this becomes an important consideration in the design of appropriate elicitation methods cognisant of any particular factors that may impede accurate reporting in these groups.

The concepts and items found in this Delphi survey to be relevant, important and feasible should be further investigated for potential inclusion in a harmonised approach to collect

participant-elicited antimalarial drug safety data. This, in turn, should improve understanding of antimalarial drug safety.

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## **LIST OF ABBREVIATIONS**

ACT	Artemisinin-based combination therapy
ADR	Adverse drug reaction
AE	Adverse event
CTCAE	Common Terminology Criteria for Adverse Events
FDA	Food and Drug Administration
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MIP	Malaria in Pregnancy (Consortium)
MMV	Medicines for Malaria Venture
NME	New Molecular Entity
SAFTEE	Systematic Assessment for Treatment Emergent Events
UCT	University of Cape Town
WHO	World Health Organization
WWARN	World Wide Antimalarial Resistance Network

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## **PART A: RESEARCH PROTOCOL**

### **DEVELOPMENT OF HARMONISED APPROACHES FOR DETECTING AND RECORDING PARTICIPANT-REPORTED**

#### **1. SYNOPSIS**

##### **Background**

The information clinical trial participants report about their health and use of non-trial treatments that become adverse event and previous/concomitant medication data is influenced by the questioning method used. There is no consensus on how participants should be questioned about these data during malaria clinical trials/studies. Following relevant methodological research we have conducted in this field we will now invite experts in antimalarial clinical drug research to work towards consensus about the appropriate design of relevant and feasible methods to question participants about their health and previous/concomitant medications.

##### **Objective**

To use a Delphi process to work towards building consensus on the appropriate methods and/or tools to use to detect adverse event and previous/concomitant medication data in malaria clinical trials/studies. The current research aims to be the beginning of dialogue among antimalarial drug clinical researchers, which would eventually lead to the development of an optimised universal AE data capturing tool in this field of research.

## **Study design and methods**

### ***Population and sampling***

Delphi panellists must meet inclusion criterion such that they have the relevant experience in the elicitation of adverse event and concomitant medication data from participants within malaria clinical trials/studies. For this study this criteria will include any of the following: clinical investigators with responsibility for a clinical trial/study where such data have been collected, those with responsibility for the selection, design, review or testing of tools to collect such data, those directly involved in the elicitation (questioning) and recording of such data from participants, those fulfilling a drug regulatory role as regards the review of clinical trial/study data, and representatives of sponsors funding and/or conducting malaria clinical studies/trials. To recruit panellists we will use purposive sampling to select appropriate participants of our recent survey about methods used in antimalarial studies/trials to elicit, assess and record these data. We will also send invitations to individuals known to us who have knowledge relevant to the research. Self-selection will ultimately determine who responds and participates. The minimum sample size we anticipate, based on Delphi-related literature, will be twenty panellists completing the last round.

### ***Delphi design, pilot and conduct***

The Delphi will be conducted online with the identity of panellists remaining anonymous to each other and the investigators to ensure that ideas, opinions and thoughts contributed by individuals are not subject to intimidation, or undue influence. There will be three to five rounds of questionnaires. The first round will consist of open-ended questions to allow participants to comment broadly on the research topic. Questions in subsequent rounds will be more specific and aim to quantify responses from preceding rounds. In each round, findings from the preceding round will be

summarised and presented to panellists and they will then be asked to comment on their level of agreement with the results. Rating will be achieved using a nine-point Likert scale with options from 'strongly agree' to 'strongly disagree' Consensus will be defined as having no less than 70 % of panellists selecting options which are within a three-point region containing the median.

***Study data management and synthesis***

Responses will be housed in suitable software. Descriptive statistics of responses to closed questions will be presented in tables or graphs, while open responses will be explored thematically.

***Ethical considerations***

The Delphi is assessed as minimal/everyday risk however concerns about confidentiality issues will be addressed by ensuring the anonymity of respondents. All panelists will be assigned unique identifiers which will be stored electronically and in paper files and be accessed by only one specific member of the research team who will not be involved in data collection and analysis. Participant's identity will not be used when reporting or publishing results of the survey.

## **2. INTRODUCTION**

### **2.1 Background**

The ACT Consortium is a group of researchers conducting projects relating to the implementation of Artemisinin-based combination therapies (ACT) for malaria treatment within Africa and Asia ([www.actconsortium.org](http://www.actconsortium.org)). The Liverpool School of Tropical Medicine has developed a customised database that will enable all relevant ACT Consortium studies, and projects outside of the ACT Consortium, to contribute their harms data. This is because the pooling of harms data may be used to generate signals of new, possibly rare, adverse drug reactions (ADRs) or identify the incidence of known ADRs with greater statistical certainty (Strom, 2005; FDA, 2005). The information about health reported by clinical trial participants in order to collect adverse event (AE) data is, however, highly influenced by questioning methods (Ioannidis *et al*, 2006). To date, there is no consensus on how participants should be questioned about their health, or how staff should then assess and/or record the data elicited. The results of individual studies, and therefore syntheses of reports, and analyses of pooled individual participant harms data are then all influenced by the methods used to collect such data. Symptoms are often elicited during unstructured discussions involving general open enquiries about health, while some projects use detailed, structured elicitation approaches, including checklists by symptom or body function. There is evidence that more detailed methods increase the sensitivity of detecting participant-reported AEs, though their effect on the nature of reports is less clear (Bent *et al*, 2006). There are concerns, for instance, that detailed methods could produce a deluge of ‘noise’, unhelpful AEs that cannot, for instance, be distinguished from background rates, and that spontaneously reported events are either more clinically meaningful or more likely to be related to a trial drug compared to placebo (Barber & Santanello, 1995; Wernicke *et al*, 2005). There is a dearth of research about

the detection and recording of participant-reported medical history and concomitant medication data in clinical trials, even though they are also integral to a safety evaluation. However, methodological studies in other areas of pharmacoepidemiology show that these data are also subject to the methods used to detect them (Strom, 2005).

Further to this, the processes which research staff use to record information about the health and treatments reported by trial participants is seldom standardised and can therefore cause further inconsistencies within or between datasets. In particular there are concerns about selection bias of participant AE reports, whereby clinical trial staff inadvertently downgrade participant reports (Basch, 2010).

Our first ACT Consortium project (SEACAT 2.5.1, UCT REC Ref: 376/2009) explored the process of participant-reported AE and concomitant medication data elicitation in two malaria and human immunodeficiency virus (HIV) drug interaction clinical trials, including whether, and if so why, certain questioning techniques fail to detect some data in this therapeutic area. Participant reports obtained through three different questioning types (a general enquiry followed by a structured enquiry using checklists of possible health issues and treatments and finally an in-depth interview) were compared. We used qualitative methods to explore participants' experiences of illness and treatment, and their reporting behaviour. There was an overall increase in the number of reports from general enquiry, through checklists, to in-depth interview. Using checklists and interviews appeared to facilitate recognition of health issues and treatments, and consideration of what to report. Information was sometimes not reported initially because participants either forgot, the event or treatment had low significance to them, it was considered not relevant, or because of perceived negative consequences of reporting. South African inpatient volunteers exhibited a "trial

citizenship”, working to achieve the researchers’ goals, compared to Tanzanian outpatients who sometimes deferred responsibility for identifying which items to report to the trial doctor. The different trial contexts appeared to cultivate some specific conditions that had a role in mediating recognition, reporting and articulation of these important variables. We proposed that some barriers to reporting in trials may be overcome by using a checklist, other barriers may require a different approach, such as counseling participants to quell potential concerns about reporting.

In a second ACT Consortium project we have surveyed methods used by antimalarial clinical drug researchers to elicit, record and assess participant-reported AEs, medical histories and treatment-use (SEACAT 2.5.1, UCT REC Ref: 376/2009). In parallel we are conducting a Cochrane systematic review that will formally assess the literature on comparisons of methods used within or specific for, clinical drug trials (in general) to elicit information from participants about AEs. We will now present a summary of the relevant literature to experts in the field of malaria clinical research and invite them to work towards consensus about the appropriate design of relevant and feasible elicitation methods to detect these important participant-reported data. This protocol describes how this will be achieved using a Delphi Process.

## **2.2 Study rationale**

Developing optimal tools with which to capture participant-reported safety data in malaria drug research requires further work. We believe it is important to locate this work within a broad framework of harmonised approaches for eliciting, assessing and recording participant-reported antimalarial safety data and this work could augment existing guidance for measuring efficacy outcomes in clinical trials (WHO, 2003).

We hope that using the Delphi will generate input and buy-in of those who could ultimately be using such harmonised methods, and also foster collaborations for the future testing of these methods. The overall project (empirical research, survey, Cochrane review and the Delphi) reflects our observations of how researchers in other therapeutic areas are working towards the same goals as regards harmonisation of methods used in recording safety or other health-related data (Booth *et al*, 2011; Basch, 2011; Woodworth *et al*, 2007). The ACT Consortium is in a good position to facilitate collaboration between those working in malaria clinical research and we consider this project to be valuable as it would enhance the field and contribute to safer use of anti-malarials in key target populations.

### **3. STUDY AIM AND OBJECTIVES**

#### **3.1 General aim**

The overall aim of the SEACAT 2.5.1 project is to contribute to the development of harmonised approaches for detecting and recording participant-reported antimalarial drug safety data.

#### **3.2 Objectives**

The objective of this specific protocol (SEACAT 2.5.1 Extension Part 3: The Delphi Process) is to select and/or design, by consensus, appropriate and feasible methods or tools for detecting participant-reported AE and concomitant medication data in a variety of antimalarial drug clinical trial/study contexts.

## **4. STUDY DESIGN AND METHODS**

### **4.1 Study design**

We will use a Delphi study to aid in the choice or design, by consensus, of appropriate and feasible methods/tools for detecting participant-reported AE and concomitant medication data in a variety of contexts, for future testing. The use of Delphi, which was developed in the 1950s by the RAND Corporation (Linstone & Turoff, 1975) involves soliciting opinion from those with relevant expertise in a particular area with the aim of achieving consensus of opinion on a particular topic. The Delphi is a multistage process characterised by controlled feedback to panellists at each round based on results of previous rounds (Sumsion, 1998). Consensus is reached through this feedback mechanism as panellists are presented with a summary of the group's perspectives along with their own. They are then asked if they would like to change their response to agree with the majority or to maintain their original opinion. A characteristic feature of the Delphi is that participants remain anonymous to each other to avoid domination by any one participant and also to allow panellists complete freedom of expression (Sinha *et al*, 2011; Boukdedid *et al*, 2011). Delphi methodology is frequently adapted according to the research aim and for practical circumstances (Booth *et al*, 2011; de Meyrick, 2003). The design for this Delphi study is largely based on the findings of two systematic reviews of Delphi methods used to determine clinical trial outcomes and health quality indicators (Sinha *et al*, 2011; Boukdedid *et al*, 2011). Other publications which offer guidelines to health researchers on how to effectively use the Delphi technique have also been used (Hasson *et al*, 2000; Sumsion, 1998; de Meyrick, 2003; Clibbens *et al*, 2011).

An advantage of using the Delphi is that panellists do not have to be in the same physical location. The process can be used to collect opinions via questionnaires

distributed remotely (Sumsion, 1998; de Meyrick, 2003). In addition, the nature of the study design ensures that individual's opinions can be considered in a non-adversarial manner allowing them to fully express themselves without reservation or fear of condemnation or ridicule (Boulkedid *et al*, 2011; Hasson *et al*, 2000). However, as selection of participants required in the process is purposive, this opens this type of study to selection bias. Furthermore, the selection of participants who have a vested interest in the study findings and who may be directly affected by the results of the Delphi may introduce subject bias as well. Because of this, it is particularly important to ensure that panellists selected for the Delphi have an interest in the research topic but remain relatively impartial so that their opinions are informed by current knowledge and practices (Hasson *et al*, 2000). Panellists for this Delphi will be selected from various disciplinary backgrounds to reduce the impact of subject bias and ensure as far as possible that true consensus is reached. In an attempt to prevent subject bias, effort will be made to include (and retain) at least 10% of panellists whose work is not directly influenced by the outcomes of the Delphi process, for instance those from regulatory agencies (Hasson *et al*, 2000).

## **4.2 Population and sampling**

### **4.2.1 Population**

Participation in the Delphi will be limited to individuals who are considered as 'experts' in the area of antimalarial clinical drug trials/studies. Participation will be limited in this way to ensure that individuals who are included as panellists have the relevant knowledge and expertise to contribute positively to the research process (Sinha *et al*, 2011; de Meyrick, 2003). For the purposes of our current research work, the term 'expert' will refer to anyone who meets one or more of the following criteria for antimalarial drug research:

- i) A clinical investigator who has had responsibility for a clinical trial/study where AE and/or concomitant medication data have been collected as part of the protocol.
- ii) Someone who has had responsibility for the selection, design, review or testing of tools to collect clinical trial/study AE and/or concomitant medication data.
- iii) Someone who is directly involved in the elicitation (questioning) and recording of AE and concomitant medication data from participants within malaria clinical trials/studies.
- iv) Someone who fulfils a drug regulatory role as regards the review of clinical trial/study data, whether pre- or post-marketing.
- v) A representative of a sponsor who has funded and/or conducted malaria clinical trials.

#### **4.2.2 Sampling**

Sampling for the Delphi will be active, using non-probability sampling techniques, specifically purposive sampling. This will enable us to ensure that those who are invited to be panellists in the Delphi will meet our inclusion criteria. The use of purposive sampling may also reduce attrition as we will mostly, but not entirely, target individuals who have a vested interest in the outcomes of the research. To try and prevent biasing the outcomes of the Delphi by including such panellists, we will try to ensure that at least 10 % of panellists are individuals who are knowledgeable on the subject matter but are not directly affected by the outcomes of the research. Survey respondents from a previous phase of this project will be assessed to determine whether or not they meet the inclusion criteria (as stated above), and invitations to take part in the Delphi will be sent to those individuals directly. Though we do not consider it feasible at this stage to invite patients (as is recommended by Sinha, 2011), their

voice will be represented by way of incorporating a summary of the results of interviews and focus group discussions held with antimalarial clinical trial participants in our ACT Project 16 Phase 1, when they were asked for suggestions as to how the clinical trial team could get the most (and accurate) information on their health and treatments.

We will also actively invite all ACT Consortium Principal Investigators (or their designee), and investigators from other antimalarial clinical research organisations, such as MiP Consortium, who are involved in clinical studies where AEs and/or concomitant medication data are elicited from participants. Contacts known to the researchers as representatives from organisations that research and develop anti-malarial drugs (e.g. Medicines for Malaria Venture, Drugs for Neglected Diseases Initiative, and pharmaceutical companies) will be approached and invited to participate. We will also send invitations to representatives from regulatory authorities known to review malaria clinical trial data.

All those identified as possible panellists will be sent an invitational email explaining the purpose of the research, what is expected of panellists and asking them to participate in the process. Self-selection by those invited will ultimately determine who responds and participates. Emails containing an automatic link to the online Delphi site will be sent to those individuals who agree to take part.

#### ***4.2.3 Sample size***

There are no clear guidelines on what constitutes a suitable sample size for a Delphi Process. Recommendations are that the researcher should be guided by the research question, resources available and the definition of what comprises an expert (Sumsion,

1998). Large sample sizes are not favourable as they raise issues with regards to data handling and potential analysis difficulties as well as resource constraints (Sumsion, 1998; Hasson *et al*, 2000) On the other hand, sample sizes which are too small may yield results which lack significance and are not very useful. It has been found that reliable outcomes in a Delphi process can be obtained with a sample size as small as twenty three panellists given that they are selected using stringent inclusion criteria (Akins *et al*, 2005). According to Akins, the sample size of a Delphi panel is not a statistically-bound parameter and good results can still be obtained using a comparatively small group of even homogenous experts. Considering our highly specific definition of an ‘expert’ and anticipating attrition at each round, we will not set a limit to the maximum number of participants who take part and no sample size calculation will be done. The intention is for the Delphi process to be as broad and inclusive as possible within the limitations set for the study population. The minimum sample size we anticipate, given criteria already mentioned, will be twenty panellists completing the last round.

### **4.3 Delphi conduct**

Questionnaires to elicit panellist opinions will be designed and administered through Surveygizmo® (or equivalent). Online completion of the questionnaires will ensure that panellists remain anonymous to each other and also to the researchers analysing the data set.

The Delphi will be comprised of an anticipated three to five rounds, each aimed at generating a higher degree of consensus among panellists about appropriate and feasible methods or tools for detecting participant-reported AE and concomitant medication data in a variety of malaria clinical trial/study contexts (Sumsion, 1998).

In the first round the group will be presented with a summary of the literature of this field of research, including our own empirical research, survey and systematic review results. Our own work may be preliminary or unpublished at the time of starting the Delphi and will be indicated as such. We consider it justifiable to include our own work in this way as there is a dearth of relevant research. This therefore ensures that novel concepts about the role of subjectivity as regards the measurement of harms data in malaria clinical research (an area devoid of evidence in the literature to date), current methods used to detect such data and the opinions of some of the malaria community about these issues are available.

In the first round, Delphi panellists will be asked open-ended questions about what they consider as optimal approach(es) for asking participants (or caregivers) about their health and use of non-study treatments to collect medical history, AE and concomitant medication data in different studies and contexts. There will be room for free-text comments and suggestions of further methods or considerations pertinent for this complex field. A draft is provided in Appendix 3, to be piloted before finalisation as indicated below.

In the second round each approach, method or component generated in the first round will be presented to panellists for rating in terms of their level of agreement of the importance and feasibility for detecting participant-reported AEs, medical history and concomitant medications. Rating will be achieved using a nine-point Likert scale with options from 'strongly agree' to 'strongly disagree'.

In subsequent rounds, each panellist will be sent a summary of the previous round's results in the form of descriptive statistics presented in tables or graphs. They will also be reminded of their own responses, and asked if they wish to revise their opinions if

they deviate from the majority, or indicate if they prefer to maintain their original opinion and state why (Clibbens *et al*, 2012). The Delphi will be stopped when consensus is achieved in each area of elicitation. Consensus will be defined (similarly to the Rand UCLA criteria for agreement as described by Fitch *et al*, 2001) as having no less than 70 % of panellists selecting options which are within the three-point region (1-3, 4-6, 7-9) containing the median (Boulkedid *et al*, 2011; Clibbens *et al*, 2012; Boulkedid *et al*, 2011).

#### **4.4 Data management**

Responses from all rounds will be downloaded from the website and housed in a suitable data management program, such as NVivo® (QSR International Pty Ltd) for qualitative data or Microsoft Excel® for quantitative data. The first round will incorporate open-ended questions which will aim to be as exhaustive as possible in exploring the concepts of interest. Relevant descriptive text will be examined for recurring ideas, which will be labelled and grouped into themes reflecting the underlying meaning or concepts behind statements (Auerbach & Silverstein, 2003; Strauss & Corbin, 1990). Descriptive statistics of responses to the closed survey questions will be presented in tables or graphs, and we will calculate median values of responses in the second and subsequent rounds.

#### **4.5 Validity and reliability**

There will be a pilot of all rounds of the survey with approximately five malaria clinical drug researchers. These individuals will be invited to log-on to the website and complete the Delphi questionnaires. Afterwards they will be contacted by a member of the research team and asked to provide feedback on the process. To help ensure face validity of the questionnaires, we will ask whether the questions made sense, were well

understood (that is to say questions were understood as intended by the researchers), unambiguous and complete (Sumsion, 1998). We will also ask the panellists to comment on whether there are additional items worth including, to help ensure content validity. Any necessary adjustments to the questionnaires will then be made. The pilot study will produce guidelines on the expected length of time it will take to fully complete the questionnaires in each round (de Meyrick, 2003). While the data elicited in the pilot will not be incorporated into the final results, the pilot group will be able to take part in the actual Delphi as this is a small field of research.

The Delphi can be time consuming and require prolonged involvement of panellists. As a result, they may lose motivation to remain in the Delphi and drop out before they complete the final round. This may result in attrition bias, especially if those who drop out have some common characteristic. The importance of completing the whole Delphi process, which may mean considerable involvement by participants, and the proposed benefit to the area of malarial clinical research of the outcome will be emphasised to panellists from the start to reduce attrition.

We will also address the issue of attrition bias by including participants with a vested interest in the current research work (malaria clinical trialists) who are directly or indirectly affected by the research question we are addressing. We will stress the importance of remaining impartial and objective in their contributions to these panellists to minimise the effect of subject bias. Panellists who do not respond by the allocated date will be prompted individually via email to ensure our response rate does not fall below the recommended 70 % in each round to ensure the rigour of the Delphi process (Sumsion, 1998).

To avoid researcher bias, the study investigators will be blinded to the identity of the panellists. Panellists will be given unique identifying codes which will only be known by a research associate who will be responsible for following up with non-responders to encourage them to complete the questionnaire at each round of the Delphi. Subject bias will be minimised by the anonymous nature of the Delphi which overcomes the biasing influences of personality, seniority, experience and group domination by individuals (Hardy *et al*, 2003).

By ensuring we maintain strict criteria in the definition of an ‘expert’, selection of panelists, heterogeneity of disciplinary backgrounds of the expert panelists and definition of consensus prior to data collection and analysis, we will add to the validity of the consensus findings of the research (Hardy *et al*, 2003).

## **5. ETHICAL CONSIDERATIONS**

### **5.1 Risks and benefits**

The Delphi process has been assessed by the investigational team as minimal/everyday risk. Notwithstanding, there may be potential concerns for respondents as regards, for instance, confidentiality. The project therefore addresses this particular concern in its introduction, and advises potential respondents that there is no obligation to take part at all and they are free to withdraw at any time. Panelists will benefit from participatory discussion with other malaria clinical trial researchers with considerable experience and expertise in this field of research. Through this discussion and sharing of information their own research and knowledge may be enhanced. A disadvantage in participating in the Delphi is that it can often be time consuming and requires commitment from panelists to complete all the rounds of the process. We have

however kept our questions as brief as possible while still ensuring the richness of data collected

## **5.2 Ethical approvals**

Written approval of this protocol will be requested from the University of Cape Town, Faculty of Health Sciences Health Research Ethics Committee before the pilot phase starts. The final version of the questionnaires to be used will be submitted to the ethics committee after the pilot phase.

## **5.3 Subject information and informed consent**

Consent to take part in this online Delphi process will be assumed as integral with its completion and submission. Therefore there is no informed consent process or documentation other than a check box at the start of the Delphi that participants signal their consent to continue.

## **5.4 Confidentiality**

Responses held on the Surveygizmo<sup>®</sup> website, or otherwise, will be kept secure (either electronically by way of password protection or through lockable physical filing systems), with access restricted to a research associate who is not part of the investigational team. Once the study is completed the panelists will be identified to the investigators in order to conduct the draw and invite them to subsequent meetings to discuss the findings. Panelists will also be asked if they would like to be acknowledged in any publication(s). However, at no point will individual responses to Delphi questions be made available to the investigators, as links between identifiers and responses will be disabled before the results are made available. At the end of the Delphi, participants will be asked if they would like their identity made available to

the investigational team, other panelists or in publications or subsequent follow-up activities.

## **6. ADMINISTRATION**

### **6.1 Adherence to the protocol**

The study will be conducted in compliance with the final version of the approved protocol. Should any additions or changes to the protocol be deemed necessary, re-approval will be requested from the research ethics committee.

### **6.2 Record keeping**

At the outset of this study the project team will set up secure electronic and paper-based filing systems to keep all study-specific information. This will be retained for 5 years after publication.

### **6.3 Publication of results**

Results are planned to be published in a peer review scientific journal with Ms Nyaradzo Mandimika as the primary author. Other authorships will be mutually agreed upon by all investigators/collaborators.

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## **PART B: LITERATURE REVIEW**

### **1. INTRODUCTION**

In 2015, malaria accounted for 438,000 deaths globally, with 90 % of these deaths occurring in the World Health Organisation Africa region (WHO, 2015). Although malaria is no longer the leading cause of death in children, having dropped from 723,000 deaths in 2000 to 306,000 in 2015 globally, it still remains a significant cause of death in children under the age of five, particularly in Sub-Saharan Africa where 292,000 deaths occurred in 2015 (WHO, 2015). Similarly, there has been a 48 % overall decrease in malaria-related mortality rates worldwide since 2000, however, it is concerning to note increasing evidence of malaria parasite resistance to many of the drugs currently being used in the fight against malaria (WHO, 2015; Hopkins-Sibley, 2014). It is estimated that African countries lose US\$ 12 billion yearly as a result of lost productivity and the gross domestic product (GDP) recedes by 1.3 % every year in the worst affected countries due to malaria disease (World Bank, 2009). Furthermore, in countries where malaria is endemic, as much as 40 % of the public sector expenditure for health is utilised for treatment of malaria (World Bank, 2009). Where individuals have to pay out of pocket to meet the cost of treatment, the cost can be as much as 25% of the monthly household income. As a result, malaria contributes significantly to poverty and reduced economic development in the hardest hit countries (World Bank, 2009).

As part of efforts to respond to the increased incidence of drug resistance, novel compounds or new molecular entities (NMEs) are being developed to meet the continued need for both the treatment and prevention of malaria (MMV, 2014; Burrows *et al*, 2014). As with all drugs, pre- and post-registration clinical trials must

be conducted to collect therapeutic efficacy and harms data in order to develop accurate risk: benefit profiles. These studies are needed to monitor for the emergence and spread of antimalarial drug resistance or fill gaps in knowledge about their use in understudied vulnerable populations that carry a high disease burden, such as pregnant women, young children or those with prevalent comorbidities.

Harms data collection aims to assess “the totality of possible adverse consequences of an intervention or therapy” and safety is inferred when there is “substantive evidence of an absence of any harm” (Ioannidis *et al*, 2006). This would mean that any recorded “untoward or unfavourable medical or psychological occurrence in a participant, including any abnormal laboratory finding, symptom or disease”, otherwise known as an adverse effect (AE), would form the basis of such evidence of harm. An AE does not necessarily have a causal relationship with the intervention or any risk associated with the research (ICH, 1996a). Although adverse drug reactions (ADRs) are widely considered to be synonymous with AEs, it is important to draw the distinction that ADRs are those harmful events for which there is a strong and well established causal link with the drug or intervention (Ioannidis *et al*, 2006).

For the assessment of safety (absence of harm), data endpoints include both objective measures (such as from clinical observations and laboratory tests) and participant-reported adverse events (AEs). These data are then assessed for potential relation to the study drug, which requires review of what is known about a participant's medical history and use of non-study medications.

There is no universal questioning method for eliciting (i.e. drawing an answer out) such data from participant reports, although there is evidence that the method used

may influence the AE data reported (Ioannidis *et al*, 2006; FDA, 1995; ICH, 1996b). Many clinical trials are not powered for a safety objective and, in particular, are unable to identify rare AEs (Seligman, 2003). In such cases, meta-analysis can be useful. This involves combining AE information from relevant studies, thus increasing the likelihood of detecting infrequent or delayed AEs which usually only occur in less than 1 in every 1000 participants (Higgins and Green, 2011; Seligman, 2003). The use of AE data collected using different elicitation methods presents a challenge in that data may not be comparable across different studies and, as such, cannot be successfully pooled in meta-analysis (Higgins and Green, 2011; Seligman, 2003).

Regulatory agencies such as the United States Food and Drug Administration (FDA) mandate that the way AEs are elicited be explicit in study reports (FDA, 1995; ICH, 1996b). However, they do not specify a particular method and, as such, the methods used to collect AE and/or non-study medication data may be variable across different studies (Bent *et al*, 2006). Development of a harmonised elicitation approach, within a particular therapeutic area like malaria, could be one way of helping with the interpretation of individual study results and pooling of data from different studies.

This review will summarise key literature related to this important topic and aims for a better understanding of the range of methods which have been used, their impact on data reports, and opinions about the optimal method. Included is the range of questioning approaches being used in general and specifically in malaria clinical research. Findings from research which compares AEs elicited when different question methods are used in clinical trials will also be described together with an overview of the rationale for the elicitation methods chosen. Finally, the review will suggest gaps

for further research. The literature review will be used to justify the need for the research conducted in this thesis, and inform the research methods used.

The work of this Delphi is located within a broader framework of harmonised approaches for eliciting, assessing and recording participant-reported antimalarial safety data. The overall project (empirical research, survey, Cochrane review and the Delphi) reflects observations of how researchers in other therapeutic areas are working towards the same goals as regards harmonisation of methods used in recording safety or other health-related data (Booth *et al*, 2011; Basch, 2011; Woodworth *et al*, 2007). The need to investigate the impact of different elicitation methods lends itself in particular to a Cochrane review methodology. Hence this literature review summarises the findings from a Cochrane review related to the current body of work which reviewed literature comparing AE elicitation methods in a systematic way. The Cochrane review process itself, revealed articles that did not involve a methods comparison and were therefore excluded, but which allowed for a description of the range of methods used and opinions about optimal methods.

## **2. LITERATURE SEARCH STRATEGY**

The search strategy used for this literature review is that used in a Cochrane systematic review of studies comparing two or more AE elicitation methods, for which I am a co-author<sup>1</sup>. Eligible studies could be comparisons within clinical drug trials themselves or experiments outside of a trial but comparing questioning methods relevant for clinical trials. An information professional assisted with the design and conduct of the search which involved the following databases: EMBASE (OVID), MEDLINE

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<sup>1</sup> Protocol published in the Cochrane Library (Allen *et al*, 2013a), the review itself is in final draft form pending submission awaiting retrieval of potentially useful papers.

(OVID), MEDLINE in Process and Other Non-Indexed Citations, the Cochrane Methodology Register (Wiley Online), the Cochrane Central Register of Controlled Trials (Wiley Online), the Cochrane Database of Systematic Reviews (Wiley Online), the Database of Abstracts of Reviews of Effects (Wiley Online), the Health Technology Assessment database (Wiley Online), CINAHL (EBSCO), CAB Abstracts (OVID), BIOSIS (Web of Knowledge), the Science Citation Index (Web of Knowledge), the Social Science Citation Index (Web of Knowledge), and the Conference Proceedings Citation Index – Science (Web of Knowledge). The key terms and concepts included: [A]: Adverse events AND measurement; [B]: Participants AND elicitation (also other synonyms for the extraction of information about adverse effects from people); [C]: Participants AND checklists (also other synonyms for the methods used to extract information about adverse effects from people). Pragmatic approaches were used to limit the search results whilst trying to maintain sensitivity. Reference lists of those articles found through the search were also assessed manually to identify additional relevant studies. The results of the Cochrane search are shown in Figure 1. Studies excluded from the Cochrane Systematic Review that offered useful information were also considered for inclusion in this literature review.

### 3. SUMMARY AND INTERPRETATION OF LITERATURE

The detail about approaches used to elicit AE data reports from study participants is rarely presented in published articles of clinical research studies (Loke & Derry, 2001).

A summary of the reference articles related to the current research are listed in Table 1 below.

**Table 1 Summary of reference articles**

Questioning method/concept	Reference articles		
<b>3.1 Range of elicitation methods for questioning trial participants about their health</b>			
a. General/open-ended enquiry	Allen <i>et al</i> , 2013b; Avery <i>et al</i> , 1967; Huskisson & Wojtulewski, 1974; Torok <i>et al</i> , 1984; Bent <i>et al</i> , 2006; Barrowman <i>et al</i> , 1970; Borghi <i>et al</i> , 1984; Spilker, 1987; Ciccolunghi & Chaudri, 1975;	Brent <i>et al</i> , 2009; Downing <i>et al</i> , 1970; Hermans <i>et al</i> , 1994; Jacobson <i>et al</i> , 1987; Nicholls <i>et al</i> , 1980; O'Connell <i>et al</i> , 2007; Perez-Lopez <i>et al</i> , 2012; Rabkin <i>et al</i> , 1992; Os <i>et al</i> , 1994	Reilly & Zbrozek, 1992; Rosenthal <i>et al</i> , 1996; Wallin & Sjovall, 1981; Wernicke <i>et al</i> , 2005; Landen <i>et al</i> , 2005; Yeo <i>et al</i> , 1991; Kruft <i>et al</i> , 2007; Monteiro <i>et al</i> , 1987; Greenhill <i>et al</i> , 2004;
b. Structured enquiry	Allen <i>et al</i> , 2013b; Avery <i>et al</i> , 1967; Huskisson & Wojtulewski, 1974; Torok <i>et al</i> , 1984; Bent <i>et al</i> , 2006; Barrowman <i>et al</i> , 1970; Borghi <i>et al</i> , 1984; Spilker, 1987; Ciccolunghi & Chaudri, 1975; Brent <i>et al</i> , 2009; Downing <i>et al</i> , 1970; Hermans <i>et al</i> , 1994;	Jacobson <i>et al</i> , 1987; Nicholls <i>et al</i> , 1980; O'Connell <i>et al</i> , 2007; Perez-Lopez <i>et al</i> , 2012; Rabkin <i>et al</i> , 1992; Reilly & Zbrozek, 1992; Rosenthal <i>et al</i> , 1996; Wallin & Sjovall, 1981; Wernicke <i>et al</i> , 2005; Landen <i>et al</i> , 2005; Yeo <i>et al</i> , 1991; Levine & Schooler, 1986	Kruft <i>et al</i> , 2007; Monteiro <i>et al</i> , 1987; Greenhill <i>et al</i> , 2004; Os <i>et al</i> , 1994; Barber & Santanello, 1995; de Vries <i>et al</i> , 2014; Sheftell 2004, Lundberg, 1980; Wallander <i>et al</i> , 1991; Wernicke <i>et al</i> , 2005
c. Other approaches	Barber & Santanello, 1995; Allen <i>et al</i> , 2013b; Kruft <i>et al</i> , 2007; Landen <i>et al</i> , 2005; Lundberg, 1980	Monteiro <i>et al</i> , 1987; Os <i>et al</i> , 1994; Wallander <i>et al</i> , 1991; Yeo <i>et al</i> , 1991;	Sheftell <i>et al</i> , 2004; de Vries <i>et al</i> , 2014; Brent <i>et al</i> , 2009; Spilker, 1987

Questioning method/concept	Reference articles		
<b>3.2 Impact of different elicitation methods on AE data collected</b>			
a. General/open-ended enquiry	Barber & Santanello, 1995; Downing <i>et al</i> , 1970;	Allen <i>et al</i> , 2013b Reilly & Zbrozek, 1992; Greenhill <i>et al</i> , 2004	Jacobson <i>et al</i> , 1987; Rabkin <i>et al</i> , 1992;
b. Structured questioning tools	de Vries <i>et al</i> , 2013 Allen <i>et al</i> , 2013b		
<b>3.3 Opinions on optimal methods for eliciting AEs</b>			
a. General/open-ended enquiry	Wernicke <i>et al</i> , 2005; Huskisson & Wojtulewski, 1974;	Barber & Santanello, 1995	
b. Structured enquiry	Wernicke <i>et al</i> , 2005		
<b>3.4 Questioning trial participants about the use of non-study medication</b>			
ICH, 1996b Ceh, 2007			

### 3.1 Range of elicitation methods for questioning trial participants about their health

There are two prominent types of elicitation methods used to ask participants about their health to collect AE data; general enquiries and structured questioning methods. The general enquiry, also known as an open-ended enquiry, spontaneous reporting or sometimes unsolicited reporting, involves asking participants a general question about their health over a particular part of the study period, such as “*Have you had any problems or felt unusual in any way since your last visit?*” (As shown in Table 1 section 3.1 sub-section a). The structured enquiry, meanwhile, uses more specific questioning, typically in reference to a list of known or suspected AEs associated with the drug (As presented in Table 1 section 3.1 sub-section b). The structured enquiry may involve the use of a tool, usually in the form of a checklist or questionnaire. An example is the Systematic Assessment for Treatment Emergent Events (SAFTEE) which was developed for detecting side-effects in psychiatric clinical trials (Levine & Schooler, 1986). In addition to these two enquiry methods, other approaches to

eliciting AE data include the use of diaries, blank forms for participants to note their symptoms, rating scales and occasionally in-depth interviews (As listed in Table 1 section 3.1 sub-section c).

### **3.2 Impact of different elicitation methods on AE data collected**

The literature search revealed that the detection of AE data across different therapeutic drug categories is influenced by a number of factors, including the elicitation, or questioning, methods used to collect information from the trial participants about their health. The Cochrane review showed that in almost all comparisons, a checklist or rating scale for collecting AE data resulted in a higher number of AEs reported when compared to a general questioning method or open-ended enquiry (the latter including a non-structured diary or blank form to complete) (Allen, EN; personal communication<sup>2</sup>). The open-ended enquiry was found to yield reports of AEs which were more clinically significant and required modification of the clinical management of the trial participants in 6 studies (As shown in Table 1 section 3.2 sub-section a). Content validation of some structured questioning tools was found to be problematic and required that participants be given clear instructions on how to interpret items listed in the tool (de Vries *et al*, 2013).

The impact of different types of questioning techniques was investigated qualitatively in one study that was relevant for malaria research (Allen *et al*, 2013b). Participants in antiretroviral/antimalarial interaction clinical trials in South Africa and Tanzania were questioned verbally about their AEs and non-study medication using a general enquiry followed by a check-list enquiry. Participants reporting differently between the two

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<sup>2</sup> Protocol published in the Cochrane Library (Allen *et al*, 2013a), the review itself is in final draft form pending submission awaiting retrieval of potentially useful papers.

methods were invited to participate in an in-depth interview and focus group discussion to explore the reasons for the contrast in reporting between the two elicitation methods. The findings confirmed that in moving from the general enquiry to the check-list (and subsequently to in-depth interviews), there was an overall increase in the number of AEs reported, as reported previously. The qualitative component of this study revealed that differences in reporting between the two questioning methods related to participants' recognition of health issues, their perceptions of what was important or necessary to report, and what they felt comfortable to reveal. Specifically, the reasons for the increase in AE reporting included forgetting to report events when asked a general enquiry and being prompted by the checklist (and to a lesser extent the in-depth interview); not reporting AEs which participants judged to be minor, less severe or irrelevant to the study; neglecting to report events out of fear of negative consequences and limited knowledge and recognition of treatment names. The different trial contexts also played a role in that fear of reporting was related to concern about being withdrawn from the trial in South Africa compared to going against the perceived "hospital rules" (mainly about the use of traditional medicines) in Tanzania.

### **3.3 Opinions on optimal methods for eliciting AEs**

Variation in AE reporting rates resulting from use of different elicitation methods date back more than forty-five years, but there remains no universally accepted questioning method or set of tools to date, even for a specific therapeutic group of compounds (Avery *et al*, 1967; Huskisson & Wojtulewski, 1974). Among researchers, there is no consensus on which method is the most appropriate for collecting AE data; each has proponents and opponents. Those who are partial to the general enquiry consider it to be a more accurate reflection of what is truly troubling the participant without biasing

their response (Wernicke *et al*, 2005; Huskisson & Wojtulewski, 1974). They are concerned that the structured enquiry artificially increases the reporting rate as it may be suggestive thereby influencing participant responses (Wernicke *et al*, 2005; Barber & Santanello, 1995). Proponents of the structured enquiry argue that this method is more sensitive as it collects AE data which participants may not report in the spontaneous enquiry because they have forgotten an event, or did not associate any change in health with the study drug among other reasons (Wernicke *et al*, 2005). They also argue that the use of a control group could be used to mitigate the higher reporting rate in the solicited (structured) enquiry group (Wernicke *et al*, 2005). The greatest challenge in using the different elicitation techniques across different clinical trials is that this could result in substantial disparities in the number and type of AEs reported, which compromises the accuracy and reliability of defining the drug's safety (and risk : benefit) profile.

These differing opinions were investigated in the survey of antimalarial drug researchers mentioned above (Allen *et al*, 2013c). The rationale for using combinations of methods or favouring one method over another included the desired “*specificity or comprehensiveness of the data sought*”, “*avoidance of suggestion of a certain response*”, the “*feasibility*” of using certain methods and determining the appropriateness of the questioning method based on their knowledge of participants’ “*perceptions about health*”. There was, however, overlap in choosing different questioning methods to fulfil the same rationale.

### **3.4 Questioning trial participants about the use of non-study medication**

Although most literature related to the issue of differential questioning methods to detect AEs, the methods used in the elicitation and recording of prior/concomitant non-

study medication data can also influence the interpretation of safety and efficacy endpoints in a clinical drug trial. Prior non-study medication will influence eligibility for a trial while concomitant non-study medication data is important due to the potential for drug-drug interactions which may have direct or indirect effects on the study drug's safety profile (ICH, 1996b). It is also important to know what (if any) non-study medications were used by trial participants to be able to consider if they caused an AE rather than the study drug (Ceh, 2007; ICH, 1996b). Lastly, eliciting indications for the use of non-study medication can also help identify unreported AEs. It is therefore equally important to specify how data on non-study medications will be assessed and recorded to avoid ambiguity and challenges in interpreting study findings at a later stage. Some of the methods used to collect and record information about non-study medication are not always accurate and unambiguous and this has the untoward effect of reducing the veracity of the study drug's safety profile (Ceh, 2007). Non-study medication information obtained through the use of explicitly defined elicitation and recording methods facilitates accurately characterising AEs, conducting causality assessments and detecting drug interactions, all of which contribute towards defining a study drug's safety profile (Ceh, 2007).

The antimalarial methods' survey mentioned above (Allen *et al*, 2013c) investigated how participant-reported non-study medication use data are elicited in drug studies. Most researchers made use of the general enquiry when asking questions about use of non-study medication with explicit reference to “*prescription only medication*”, “*over-the-counter medication*”, “*traditional medication*”, “*supplements*” and “*vaccinations*”. Researchers also incorporated pictorial questioning tools such as pictures, diagrams and pictorial diaries either alone or in combination with general or structured enquiry. When used in combination, pictorial tools were thought to augment the general and/or

structured enquiry as they could enhance understanding, particularly in low literacy settings (Allen *et al*, 2013c). Structured questions, meanwhile, were considered useful for revealing specific medicines such as recent prior use of antimalarials. The qualitative study nested within these antimalarial/antiretroviral interactions trials found that the number of non-study medication reported also increased as the elicitation methods became more detailed or intensive (Allen *et al*, 2013b). The reasons were similar as for AEs; more detail helped participants recognise what the investigators considered as medicines and that reporting use of these was relevant for the trial.

#### **4. IDENTIFICATION OF GAPS AND JUSTIFICATION FOR FURTHER RESEARCH**

As there is still no consensus about optimal methods for eliciting participant-reported AE and non-study medication data in malaria clinical studies, despite their influence on the data collected, there is need for further research in this area. The ideal approach to finding the optimal elicitation method is unclear as this is a complex field. However, a good approach for achieving consensus about this topic among researchers is a Delphi study, as it is specifically designed to solicit opinion from those with relevant expertise in a particular area with the aim of achieving consensus on a particular topic. The current research, conducted as part of the requirements for the degree Master of Public Health, expands on the previous work summarised above, which initiated a dialogue on the development of harmonised elicitation approaches for antimalarial clinical studies (Allen *et al*, 2013c). This dialogue will now be continued through the use of a Delphi process with antimalarial drug clinical researchers to work towards the design of appropriate and feasible methods or tools for detecting participant-reported AE and non-study medication data in uncomplicated antimalarial drug studies. This

will be achieved by working on generating consensus among a group of experienced and knowledgeable antimalarial drug researchers on potential methods and tools.

It is particularly important to optimise methods for accurately assessing the safety of antimalarials because many drug regimens currently in use are relatively new and yet are already being deployed widely, even in vulnerable at-risk populations without malaria as preventive treatment or for transmission blocking (MMV, 2014; Burrows *et al*, 2014). Defining their safety profiles accurately is thus important to help to inform clinical practice, and could boost efforts to enhance the acceptability of new drug treatments in the target populations. Harmonised elicitation methods could help with the interpretation of individual studies but also to enable valid pooling of AE data across different studies (with similar contexts), which in turn would help in identifying rare AEs and their risk factors.

## **5. CONCLUSIONS**

The reviewed literature showed that the use of different elicitation methods to question participants about their health and use of non-study medication in clinical studies, in general and specifically in malaria, can influence safety outcome data. Although it is widely accepted that there is a need to standardise these methods across different studies, there is limited evidence of efforts towards developing such universal methods and tools. The use of standardised methods would facilitate valid pooled analysis of individual AE data across different studies in meta-analysis. This could ultimately lead to the development of more accurate and reliable drug safety profiles to inform clinical practice. While this issue is pertinent to any drug, there is a specific need to explore the optimal methods for eliciting these data in malaria clinical research given the widespread use of antimalarials for treatment, disease prevention and transmission

blocking. The harmonisation of AE and non-study medication elicitation methods will enhance our ability to characterise the safety profile of the novel antimalarials that are urgently needed given the alarming spread of drug resistance to all currently available antimalarials (Ashley *et al*, 2014; Tun *et al*, 2015; WHO, 2013).

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**PART C: JOURNAL MANUSCRIPT**

*For submission to Malaria Journal*

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**Working towards consensus on methods used to elicit participant-reported safety data in uncomplicated malaria clinical drug studies: A Delphi Process.**

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## 1. ABSTRACT

**Background:** Eliciting adverse event (AE) and non-study medication reports from clinical research participants is integral for evaluating drug safety. However, using different methods to question participants yields inconsistent results, compromising the interpretation, comparison and pooling of data across studies. This is particularly important given the widespread use of antimalarials in vulnerable populations, and their increasing use in healthy but at-risk individuals as preventive treatment or to reduce malaria transmission.

**Methods:** Experienced, qualified antimalarial drug clinical researchers were invited to participate in a Delphi process, to facilitate consensus on what panellists consider to be optimal (relevant, important and feasible) methods, tools, and approaches for detecting participant-reported AE and non-study medication data in uncomplicated malaria treatment studies.

**Results:** Of the 72 invited, 25; 16 and 10 panellists responded to the first, second and third rounds of the Delphi process respectively. Overall, 68% (68/100) of all questioning items presented for rating achieved consensus. When asking general questions about health, panellists agreed to include a question/concept about any change in health, taking care to ensure that such questions/concepts do not imply causality. Eighty-nine percent (39/44) of structured items about specific signs and symptoms, were rated as optimal. For non-study medications, a general question and most structured questioning items were considered an optimal approach. The use of mobile phones, patient diaries, rating scales as well as openly engaging with participants to discuss concerns were also considered optimal complementary data-elicitation tools.

**Conclusions:** This study succeeded in reaching consensus within a section of the antimalarial drug clinical research community about using a general question concept,

and some structured questions for eliciting data about AEs and non-study medication reports. The findings suggest that one method of questioning may not be superior to another, or sufficient to fulfil its purpose on its own and that the use of a combination of methods may be optimal. The concepts and items considered found in this Delphi survey to be relevant, important and feasible should be further investigated for potential inclusion in a harmonised approach to collect participant-elicited antimalarial drug safety data. This, in turn, should improve understanding of antimalarial drug safety.

**Key words:**

Elicitation methods, clinical trials, safety, adverse events, non-study medication, Delphi.

Word count: 350 (max permitted 350).

## **2. BACKGROUND**

Malaria is one of the greatest public health challenges in the tropics. In 2015 the World Health Organisation reported an estimated 214 million malaria cases globally, with an estimated 438 000 malaria-related deaths [1]. The disease is most prevalent in Africa with pregnant women and young children, mostly under five years, being the most vulnerable [1]. In countries where malaria is endemic, as much as 40 % of the public sector expenditure for health is utilised for treatment of malaria [2]. Where individuals have to pay out of pocket to meet the cost of treatment, the cost can be as much as 25 % of the monthly household income. As a result, malaria contributes significantly to poverty and reduced economic development in the hardest hit countries [2].

An integrated approach to controlling malaria is thus essential in stemming the tide and impact of this disease, incorporating prevention (including preventive chemotherapy) as well as prompt and effective treatment of infections with efficacious medicines (WHO, 2015). Efforts to control and eventually eliminate malaria have resulted in the widespread use of artemisinin-based combination therapies (ACTs) as the first line treatment for uncomplicated malaria [3, 4].

As part of efforts to eradicate malaria and stem the development of resistance to antimalarial treatment, novel compounds or new molecular entities (NMEs) are being developed to meet the continued need for both the treatment and prevention of malaria [5,6]. Before these can be marketed for use in the general population, they must first be assessed in clinical trials to establish their efficacy and safety profiles. Due to inherent limitations of clinical trials to fully assess safety, more studies are then conducted post-licensure to continue to build knowledge about adverse drug effects (and effectiveness) in real-world contexts and vulnerable populations excluded from

clinical trials. Pooling safety data collected during numerous clinical studies facilitates the more accurate definition of the nature and risk of adverse effects. In so doing, there is an increased likelihood of the identification of sub-populations at greater risk, and of detecting infrequent or delayed effects. These are usually only detected with large sample sizes (ordinarily >1000 study participants) and may be missed when smaller cohorts are used [7]. Using synthesised datasets to better define the safety of new antimalarial drugs and existing drugs in understudied populations is therefore important, especially where the harm: benefit balance may be shifted when these are used in asymptomatic or uninfected people to prevent malaria or reduce malaria transmission.

Regulatory agencies require the method of collecting safety data to be explicit in study reports because of its potential impact on the study results, and, furthermore, that methods should be standardised within drug development programmes [8]. However, they do not in general specify which methods to use, and the word count constraints in publications may preclude sufficiently detailed description of these approaches and tools [9]. This compromises the interpretation of individual studies and subsequent systematic reviews or meta-analyses [7, 10].

Drug safety and tolerability profiles are generated by gathering adverse event (AE) data which are then considered for any potential relationship to the study drug using what is known about a participant's medical history and use of non-study medication. Objective AE assessments include medical examinations and laboratory tests which are likely to be standardised within and between studies [11]. Studies also rely on subjective AE reports that are obtained directly from trial participants by asking them about their health status over a defined period of time. The impact of the questioning

(elicitation) method on safety data is considered to be an important issue that has not received enough attention [12, 13]. A systematic review of studies in any therapeutic area that compared elicitation methods, reveals that more detailed questioning (such as with checklists or rating scales) increases the number of AEs reported compared to an open-ended or general enquiry (Protocol published in the Cochrane Library [14], the review itself is in final draft form). Proponents for a general enquiry believe it collects data which is more clinically meaningful even though it may be less sensitive [15]. An argument against the structured enquiry reflects concerns that it artificially increases the AE reporting rate as it may be suggestive, thereby biasing participant responses [16]. Structured methods may also be more time consuming and less feasible to conduct in practice. Proponents of the structured enquiry, meanwhile, argue that this method is necessarily more sensitive as it detects AE data which participants do not report spontaneously [17]. For malaria specifically, there is evidence that when participants forgot an event, or did not consider it significant or relevant when asked on general enquiry, a checklist enquiry prompted an AE report [18]. There may also be influence from the study context on reporting of AEs, medical history and non-study medications that are not overcome by a tool, for instance where participants fear the consequences of reporting [18].

A survey of antimalarial drug clinical researchers found that, for capturing AEs in intervention studies, most researchers used a combination of a general and structured enquiry (31%) or structured enquiry only (26 %) with less using a general enquiry alone (18 %) [18]. A minority of researchers incorporated tools involving pictures [19]. Most researchers in the survey use a general enquiry when asking questions about use of non-study medication with explicit reference to, for instance, “*prescription only*

*medication*”, “*over-the-counter medication*”, “*traditional medication*”, “*supplements*” and “*vaccinations*” [18].

The aim of this research is to seek consensus among a panel of antimalarial drug clinical researchers about which methods they consider optimal (relevant, important and feasible) for eliciting AE and non-study medication data from participants in uncomplicated malaria drug studies. This is expected to contribute to the development of a harmonised approach that may, in turn, facilitate more accurate interpretation or pooling of participant-elicited safety data from multiple studies.

### **3. METHODS**

#### **3.1 The Delphi**

A Delphi process was selected as its aim is to achieve consensus on a particular topic. This method was developed in the 1950s by the RAND Corporation and involves soliciting opinions from a panel of knowledgeable individuals with relevant experience and expertise in a particular area. Successive rounds of questioning about a topic are conducted after individual results from the previous round are reported back to the group for consideration [20]. Panellists remain anonymous to each other to avoid domination by any one individual and to allow for freedom of expression without reservation or fear of condemnation or ridicule [21, 22, 23]. Typically the length of a Delphi study varies from three to five rounds and is dependent on the degree of consensus required by the investigators and the criterion chosen to define consensus [22, 24].

Questionnaires (Questionnaires included as additional files under Appendix I) to elicit panellist opinions were designed and pilot tested before they were administered online

through SurveyGizmo® so that panellists did not have to be in the same physical location, and could complete each survey at a convenient time [25,26].

In the first round panellists were presented with a summary of relevant literature, and were asked open-ended questions about what they considered the optimal method(s), concept(s) and/or approach(es) for asking study participants (or caregivers) to collect subjective AE and non-study (previous/concomitant) medication data (Participant Information Sheet and Literature and Survey Results Summary included as additional files under Appendices II and III respectively). Space was provided for free-text comments and suggestions of further methods or considerations pertinent to this complex field.

In round two, specific phrases suggested by pannelists in round one were then assessed in terms of their underlying meanings and categorised into questioning concepts for rating in subsequent rounds as regards their relevance, importance and feasibility, i.e. to be optimal they should fulfil all three criteria as all would be appropriate for malaria clinical research for detecting participant-reported AEs and non-study medication. The definition of consensus in Delphi process studies varies. For this study, each component was considered to have reached consensus when at least 70 % of panellists selected options within a three-point region of a nine-point Likert scale containing the median indicating that most panellists disagree (score 1–3), are uncertain (score 4–6), or agree (score 7–9) that a given item is optimal [22, 27, 28]. Individual items were not mutually exclusive – for example, panellists could recommend both a general enquiry and a structured enquiry method.

Comments, suggestions and further methods were paraphrased into short descriptions

and panellists were advised that the wording of questions or items themselves were only examples of possible phrases/words and that exact terminology may be context-specific or adapted for ensuring local understanding of the question by study participants. The intention was for participants to consider the concepts behind the general questions rather than evaluate the questions themselves, hence the inclusion of some illustrative examples. For instance, they were asked to rate the following types of general question concepts (with examples) that may be posed to participants in an antimalarial study: "General question about feeling (*e.g.* 'How have you [has your child] been feeling?')". This approach was applied throughout the Delphi, where appropriate. Similarly, an example of a structured approach was "Questions about body parts, systems or functions (*e.g.* *Have you experienced a problem with your head, chest, breathing?*)". Rating was achieved using a nine-point Likert scale with options ranging from 'strongly agree' to 'strongly disagree'.

In the third and final round, each panellist was sent descriptive statistics summarising responses from round two and a copy of their individual responses. Items which achieved consensus in round two were presented in a summary at the beginning of round three but were not submitted for reassessment. For items that had not achieved consensus they were asked whether or not they wished to change their opinion/rating in light of the summary information from all panellists [27].

#### **4. STUDY POPULATION AND SAMPLING**

##### **4.1 Population**

Participation was limited to individuals with experience and knowledge of clinical antimalarial drug studies to ensure they could contribute constructively to the process

[21, 25]. All panellists needed to meet one or more of the following criteria:

- (i) A clinical researcher who has been responsible for a clinical trial/study where AE and/or non-study medication data was collected as part of the protocol.
- (ii) An individual who has been responsible for the selection, design, review or testing of tools to collect clinical trial/study AE and/or non-study medication data.
- (iii) An individual who has had direct involvement in the elicitation and recording of AE and non-study medication data from participants within malaria clinical trials/studies.
- (iv) A regulatory authority responsible for reviewing clinical trial/study data, whether pre- or post-marketing.
- (v) A representative of a sponsor who has funded and/or conducted malaria clinical trials.

## **4.2 Sampling**

Sampling was purposive to ensure that those who were invited met the inclusion criteria, and was largely from those who had taken part in a previous survey [29]. Individuals from organisations well known for researching or developing anti-malarial drugs were also approached. Self-selection by those invited ultimately determined who responded and participated in each of the rounds. In an effort to ensure that panellists who could be directly impacted by the results of the Delphi would remain objective in their review of other panellists' opinions, the importance of remaining impartial and objective in their contributions was emphasised.

## **4.3 Sample size**

The sample size of a Delphi panel is not a statistically-bound parameter and good

results can still be obtained using a comparatively small group of even heterogeneous experts [30]. Some Delphi studies have shown results can be obtained using panels with as few as 5 or 6 panellists while other studies have used panels with as many as 1 685 panellists [30]. Ultimately, the size of a Delphi panel is determined by the availability of panellists with the relevant qualities and expertise [31]. Considering our highly specific inclusion criteria and anticipated attrition at each round, there was no limit set to the maximum number of participants who could take part, and no sample size calculation was done. There was no explicit intention on a specific number for the minimum sample size, however the minimum sample size anticipated, based on Delphi-related literature, was approximately twenty panellists completing the last round of the Delphi [30].

#### **4.4 Data management and analysis**

Responses were downloaded from SurveyGizmo<sup>®</sup> and analysed using Microsoft Excel<sup>®</sup>. The two main sections, Section A (Adverse Events) and Section B (Non-study Medication) were each further sub-divided to include three sub-sections on general questioning items, structured question items and pictorial and/or physical questioning tool items (Questionnaires included as additional files under Appendix I). Consensus was assessed individually per item included in the questionnaires, and overall per sub-section.

#### **4.4 Ethical considerations**

Written approval to conduct the study was obtained from the Human Research Ethics Committee of the University of Cape Town's Faculty of Health Sciences. The first page of the Delphi specified "*If you would like to continue with the Delphi please enter your email address below and continue on to the next page. Please note that by*

*continuing we will assume you have given consent to take part*". The investigators were blinded to each participant's identity during data collection and analysis. Access to the responses was password protected and limited to members of the investigation team. Once the final round of the Delphi process was closed the survey was deactivated, and links between email addresses and the website were disabled.

## **5. RESULTS**

A total of seventy-two researchers were invited to participate, of whom 25 (35%) completed round one. In round two all panellists who had completed round one were re-invited. Of these, 16/25 (64%) responded, with fifteen fully completing the round and one panellist partially completing the questionnaire. In the final round all who had fully completed round two were invited and 10/15 (67%) responded.

### **5.1 Study participants**

The study population was comprised mostly of panellists who met at least two of the inclusion criteria. Of the 25 participants in round one, 18/25 (72%) had been responsible for the selection, design, review and/or testing of tools, 16/25 (64 %) had five or more years of experience in malaria clinical studies and a further 3/25 (12%) had 1 - 5 years of experience.

Panellists came from seventeen countries, with over half (14/25) coming from malaria endemic countries. Most countries represented had one panellist [Australia, Bangladesh, Burkina Faso, Denmark, Gabon, Gambia, Kenya, Malawi, Mali, Nigeria, Tanzania, Uganda, the United Kingdom] but some had more than one [United States of America (USA) (2), Zambia (2), Ghana (2) and Belgium (3)].

## 5.2 Assessment of consensus

The percentage of all items reaching consensus overall rose from 24 % in round two to 68 % in round 3 (Table 2). The majority of items reaching consensus in round two were structured questions about signs and symptoms and non-study medication.

**Table 2 Overall number of questions reaching consensus by sub-section**

Elicitation methods	Number of items	Items reaching Consensus		
		Round 2	Round 3	Total
<b>Adverse events</b>				
General questions	5	1	1	2 (40%)
Structured questions about body parts, systems or function	11	0	3	3 (27%)
Structured questions about signs and symptoms	44	16	24	40 (91%)
Pictorial questioning tools	14	0	2	2 (14%)
Other	8	1	4	5 (63%)
<b>Non-study medication</b>				
General questions	1	1	N/A	1 (100%)
Structured questions	11	5	5	10 (91%)
Pictorial and/or other physical tools	5	0	4	4 (80%)
Other	1	0	1	1 (100%)
<b>Total</b>	<b>100</b>	<b>24</b>	<b>44</b>	<b>68 (68%)</b>

## 5.3 Asking participants about AEs

Panellists agreed that an explicit question about change in health (e.g. 'Have you observed any change or new complaint since your last visit/ in the past x days [trial-specific time scale]?') was optimal for asking about AEs during malaria clinical trials. They also agreed that a general question implying causality should be avoided (e.g. 'Did your child experience any side effect from the drug since your last visit/ in the past x days [trial-specific time scale]?'). Consensus could not be reached on items

pertaining to the general questions asking about how a study participant was feeling (e.g. 'How have you [has your child] been feeling since your last visit/ in the past x days [trial-specific time scale]?), whether they had had past adverse reactions to treatments (e.g. 'Have you ever reacted badly to a drug or vaccine') or how they rated any change in health (e.g. 'How do you rate your state of health after taking the study medicine?').

Table 3 Summary of consensus status for individual questioning items\*

ITEMS RATED FOR RELEVANCE, IMPORTANCE AND FEASIBILITY	CONSENSUS STATUS	
<b>SECTION A:</b>		
<b>GENERAL QUESTIONS ABOUT AEs</b>	<b>Round 2</b>	<b>Round 3</b>
Explicit question about change in health (e.g. 'Have you observed any change or new complaint since your last visit/ in the past x days [trial-specific time scale]?')	Include	
Question implying causality (e.g. 'Did your child experience any side effect from the drug since your last visit/ in the past x days [trial-specific time scale]?')		Exclude
General question about feeling (e.g. 'How have you [has your child] been feeling since your last visit/ in the past x days [trial-specific time scale]?')		No consensus
General question about past adverse reactions to treatments (e.g. 'Have you ever reacted badly to a drug or vaccine').		No consensus
General question about rating any change in health (e.g. 'How do you rate your state of health after taking the study medicine?').		No consensus
<b>STRUCTURED QUESTIONS ABOUT BODY PARTS, SYSTEMS OR FUNCTION</b>	<b>Round 2</b>	<b>Round 3</b>
Nose		Include
Lungs/breathing		Include
Head		Include
Ears		No consensus
Throat		No consensus
Eyes		No consensus
Chest		No consensus
Heart		No consensus

<b>STRUCTURED QUESTIONS ABOUT BODY PARTS, SYSTEMS OR FUNCTION (CONT.)</b>	<b>Round 2</b>	<b>Round 3</b>
Nervous system		No consensus
<b>STRUCTURED QUESTIONS ABOUT SIGNS AND SYMPTOMS</b>	<b>Round 2</b>	<b>Round 3</b>
Tiredness/ fatigue/ weakness/ lethargy		Include
Muscle pain		Include
Joint pain		Include
Abdominal pain		Include
Mood/ behavioural change		Include
Allergic skin rash (e.g. some forms of urticaria)		Include
Skin abnormalities		Include
Dizziness		Include
Vision/sight problem		Include
Change in urine colour		Include
Palpitations		Include
Confusion		Include
Jaundice/icterus		Include
Oculogyric crisis		Exclude
Photosensitivity (sensitivity to light)		Include
Spontaneous bleeding		Include
Constipation		Include
Blisters (on skin or mucous membrane)		Include
Hallucinations		Include
Headache	Include	
Fever	Include	
Cough	Include	

STRUCTURED QUESTIONS ABOUT SIGNS AND SYMPTOMS (CONT.)	Round 2	Round 3
Loss of appetite	Include	
Vomiting	Include	
Nausea	Include	
Diarrhoea	Include	
Itching (no rash)	Include	
Peeling skin	Include	
Tinnitus (ringing in the ears)/ hearing problem	Include	
Sleep disturbance/ nightmares	Include	
Involuntary movements (e.g. rigors/ convulsions/ seizures)	Include	
Wheezing/ difficulty breathing	Include	
Non-allergic skin rash (e.g. scabies)		No consensus
Posturing		No consensus
Pallor		No consensus
Change in walking (gait disturbance)		No consensus
<b><i>In infants:</i></b>		
Eating/drinking/ feeding less than normal	Include	
Irritable		Include
Abnormal sucking, if breastfed		Include
Crying more than normal		Include
Difficult to arouse	Include	
<b><i>In pregnant women:</i></b>		
Baby movements less than normal		Include
Vaginal bleeding		Include
Increased uterine contractions, more than normal	Include	

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**PICTORIAL QUESTIONING TOOLS ABOUT AEs****Round 2****Round 3**

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*Using photographs, drawings or pictures of the following signs and symptoms:*

Mucous membrane blisters

Include

Skin rash

Include

Headache

No consensus

Fever

No consensus

Loss of appetite

No consensus

Diarrhoea

No consensus

Jaundice/icterus

No consensus

Joint pain

No consensus

Pruritus

No consensus

*Using photographs, drawings or pictures of the following body parts:*

Respiratory system

No consensus

Gastrointestinal tract

No consensus

Central nervous system

No consensus

Skin

No consensus

Whole body outline

No consensus

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<b>OTHER</b>	<b>Round 2</b>	<b>Round 3</b>
Collecting AE reports using mobile phones		Include
Collecting AE reports using patient diaries		Include
Using an archive of visual analogue scales from day 0 throughout all the follow-ups to measure potential AEs and any change in the occurrence of these events.		Include
Openly engaging participants to discuss any concerns they have		Include
Keeping an archive of digital photographs of AEs	Include	
Collecting AE reports using group discussions		No consensus
Using flip charts, with a picture on one side for the participant and a written question for the investigator on the reverse side (to reduce investigator variability).		No consensus
Using video footage on smartphones or tablets to show how some AEs which are difficult to depict on still images may manifest e.g. seizure activity.		No consensus
<b>SECTION B</b>		
<b>GENERAL QUESTIONS ABOUT PREVIOUS OR CONCOMITANT MEDICATION (NON-STUDY DRUG)</b>	<b>Round 2</b>	<b>Round 3</b>
General questions about the use of non-study medications (e.g. 'Have you taken any medications since your last visit/ in the past x days [trial-specific time scale]?').	Include	
<b>STRUCTURED QUESTIONS ABOUT PREVIOUS OR CONCOMITANT MEDICATION (NON-STUDY DRUG)</b>	<b>Round 2</b>	<b>Round 3</b>
<i>Questions about the source of medicines:</i>		
Medicine obtained from another health facility	Include	
Medicine obtained from a drug shop, pharmacy, chemical seller, the market (or equivalent)	Include	
Medicine obtained from a traditional healer, informal doctor (or equivalent)	Include	

<b>STRUCTURED QUESTIONS ABOUT PREVIOUS OR CONCOMITANT MEDICATION (NON-STUDY DRUG) (CONT.)</b>	<b>Round 2</b>	<b>Round 3</b>
Medicines already available in the home (from previous treatment courses).	Include	
Medicines obtained from family and/or friends		Include
Collecting and using naturally occurring herbs/remedies	Include	
<i>Structured questions about treatment class or specified indication:</i>		
Analgesics/ anti-inflammatory drug		Include
Antibiotics		Include
Antihistamines		Include
Antimalarial		Include
Vitamins		No consensus
<b>OTHER</b>	<b>Round 2</b>	<b>Round 3</b>
Please rate the following statement to reflect the extent to which you feel it is relevant and important and feasible for collecting non-study medication data. <i>"Participants should be asked about individual treatments by name according to what is known to be locally relevant?"</i>		Include
<b>PICTORIAL AND/OR OTHER PHYSICAL TOOLS TO QUESTION ABOUT PREVIOUS OR CONCOMITANT MEDICATION (NON-STUDY DRUG)</b>	<b>Round 2</b>	<b>Round 3</b>
Showing photographs or drawings of commonly used drugs or drug packets		Include
Showing samples of commonly used drugs or drug packets		Include
Showing photographs or drawings of commonly used herbs/traditional remedies		Include
Asking participants to bring any non-study medication they may have taken before and/or during the trial/study to scheduled visits for a physical inspection		Include
Showing samples of commonly used herbs/ traditional remedies		No consensus

\* Summary of consensus status for individual questioning items rated for relevance, importance and feasibility for asking participants in uncomplicated malaria clinical trials/studies about adverse events and non-study medication.

Few specific questions about body parts, systems or functions achieved consensus about whether or not they should be included in structured questioning (3 of 11 possible items) (Table 3). However, 90 percent (40/44) of specific signs and symptoms achieved consensus; 39/40 of these were rated as being optimal for inclusion with one (oculogyric crisis) recommended for exclusion (Table 3).

Consensus was also reached for showing study participants pictures or photos of ‘mucous membrane blisters’ and ‘skin rash’ to elicit reports, with no other body parts being recommended for inclusion in this format. Panellists also agreed that collecting AE reports using mobile phones or patient diaries, using an archive of visual analogue scales or digital photographs of AEs and “openly engaging participants to discuss any concerns they have” were all ideas that should be considered (Table ).

#### **5.4 Asking participants about non-study medication use**

Panellists agreed that asking a general question about the use of non-study medications (e.g. 'Have you taken any medications since your last visit/ in the past x days [trial-specific time scale]?') was optimal, as were, in addition, all but one of the eleven structured questioning items on source of medicines, treatment class or specified indications (Table ). The one item which failed to achieve consensus was whether or not items about “*vitamins*” as a treatment class were optimal. Panellists could also not agree whether to include or exclude the option of showing samples of commonly used herbs or traditional remedies specific to the study context. However, they did agree that participants should be asked about individual treatments by name according to what is known to be locally relevant.

## **6. DISCUSSION**

This study builds on previous work aimed at working towards the development of harmonised tools for asking antimalarial clinical research participants about any potential adverse events and use of non-study medication. The results suggest that a combination of questioning methods is considered optimal for enhancing the reporting of these data in uncomplicated malaria treatment studies. The specific items which achieved consensus may be considered for inclusion in the development of harmonised approaches for data collection. Some items that did not achieve consensus for use could still be useful in some contexts and as such should rather be considered on a study by study basis.

Consensus was achieved among panellists that, when asking general questions to capture subjective AE reports, it should be clear that the enquiry is about a change in health but does not imply that participants consider the study drug as the cause of the change. These concepts, when carefully phrased, are likely to allow participants to report any new medical occurrence without suggesting that he/she try to associate their experience with the study drug. This would be consistent with a tenet of assessing drug safety, capturing AEs regardless of whether or not they are thought to be attributed to the drug [32]. While investigators have been aware of this for decades, it is important to be careful about phrasing an open question about health to help ensure that study participants do not unwittingly filter information during reporting. To overcome this, some teams ask staff to use a standard phrase [29]. The concept of an ideal phrase for general questions postulated through this Delphi study should prove useful to guide trial teams in designing their AE elicitation methods, and could be used to achieve consistency within and between trials. Alternatively, should staff be allowed to paraphrase these concepts, they should be trained to be fully understand the rationale

and potential implications of subtle changes in wording. Open engagement with participants to discuss any concerns they may have was also considered useful by the panellists to help overcome any preconceptions about the negative consequences of reporting. When designing and implementing question approaches there should be cognisance of the literature relating to health communications, and work already conducted with clinical research staff who question malaria patients about AEs [19,33,34].

In recent work focused on antimalarial research, investigators were able to develop novel questioning tools and processes which could be accurately administered by non-clinicians. In particular, there was a focus on encouraging free sharing of information between the participant/patient and investigator/reporter by increasing trust and consensus in the process, in addition to encouraging equal responsibility between the two parties in reporting AEs [19]. Other work in the health communications field implores professionals to remain cognisant of the variety of lay people's definitions of drugs/medicines and this would include a consideration of the potential impact of any discrepancies of AE reporting [35].

There was also agreement, however, between the Delphi panellists about optimal structured questions to elicit AE reports, presenting various signs and symptoms for participants to consider. General and structured questions are therefore not necessarily mutually exclusive. As shown by previous studies, a structured approach is likely to increase the sensitivity of detecting AEs, some of which may have been forgotten or not considered relevant or important by participants [13, 18]. While this may increase the workload for trial staff, using a list will ensure standard practice within and between study teams. Any such list will, however, require further refinement as there

was overlap between some items identified as optimal (e.g. several skin conditions were considered for inclusion in a questioning tool individually and also as a general term). Panellists also suggested using digital photos of AEs (e.g. of ‘mucous membrane blisters’), to complement the lists.

A higher degree of consensus was achieved with the questioning sub-section pertaining to eliciting non-study medication reports compared to AE reports. It may be that there is less controversy about whether different questioning methods impact on the data for non-study medication exposures than AEs, with a smaller potential for these questions biasing responses. The data are inherently different - AEs being more subjective experiences, while taking a non-study medication being a more concrete occurrence. However, from a study participant's perspective, there may be different perceptions of what constitutes a medicine, so giving definitions and examples can avoid misunderstandings [35]. Consistent with the findings relating to AE reports, panellists also agreed that non-study medication data should be elicited using general questions. Structured questioning tools could however be used in conjunction with general questioning items to ensure that trial participants do not inadvertently omit information about their use of medication (particularly over the counter, traditional, alternative or complementary medicines) based on their own understanding of what constitutes a medicine. As it is unlikely to be feasible to have an exhaustive list of medicines, combining a general and more specific question will allow for capturing items not mentioned on a list. As for AEs, the details of optimal permutations that should be used when developing a harmonised approach were not resolved during the Delphi, which rather achieved a basket of potential options to consider for inclusion.

In relation to non-study medication use data, consensus was reached that participants in clinical trials should be asked about individual treatments by name (and treatment class) according to what is relevant in the local context. In some instances the indication for which the non-study medication was taken could identify an unreported AE which may have resulted from taking the study medication [36]. All the proposed questioning items pertaining to the source of medication (for example a health facility, traditional healer; chemical seller, family and/or friends) achieved consensus. Asking about the source of medicines may alert the researcher of what participants consider to be medicine, and vice versa, and this could be particularly important in communities where the use of alternative and/or traditional medicines or remedies is widespread and common practice. In some contexts, there may be reluctance to volunteer some information, such as traditional therapies. There should be discussion within the team, therefore, as to how to encourage participants to feel comfortable enough to report those items without fear of negative consequences, such as being admonished by investigators for using such non-study medication. However, in some clinical trials admitting their use could result in their being ineligible for inclusion, when it would be important to compensate participants for their time thus far and ensure prompt effective case management either by the study team or nearby health facility. If participants are already enrolled in a study, eliciting all non-study medication data is essential for assessing causality and describing the safety and tolerability profile of the study drug(s). Thus it is preferable to retain the participant in the intention to treat population rather than withdraw the participant, unless this would put the participant at increased risk.

The findings suggest that one method of questioning may not be superior to another, or sufficient to fulfil its purpose on its own, for eliciting important data about health

and use of non-study medication. It is therefore likely that a combination of questioning methods, augmented by openly engaging with participants to ensure they feel open to share their experiences without fear of reprimand, may be the optimal approach in malaria clinical research. Thus, the details of optimal permutations not resolved during the Delphi and refinement of this basket of potential options, should now be taken forward for further discussions within the anti-malarial drug research community. This could be done at the time of international meetings with those interested malaria researchers, ideally joined by health communications specialists and those who have experienced malaria as a patient.

## **7. LIMITATIONS**

Due to respondent fatigue and time constraints the Delphi was terminated before consensus on all items could be established. While consensus for those unresolved items may have been achieved in further rounds, this is not necessarily the case. The lack of consensus on these items indicate that those items are not widely considered optimal. This may reflect the complexity of the topic, which is likely further confounded by the differing contexts in which the panellists conduct research. The time lapse between rounds of the Delphi ranged between three to six months. This may have contributed to the attrition rates between rounds and may have reduced the quality of responses. The length and complexity of the survey, including the composite concept used for the definition of 'optimal', may have further contributed to the attrition between rounds. Arguably 'importance' and 'feasibility' are different notions and participants may have felt it difficult to try and consider them together. The panellists who completed all three rounds were similar in their background and experience, which may have biased the findings towards the opinions of a select few. During round one, a participant suggested the inclusion of oculogyric crisis for rating in subsequent

rounds. This indicated that there may have been some misunderstanding of the concept of “participant-reported” AEs.

## **8. RECOMMENDATIONS**

This online Delphi process showed that it is possible to engage multiple antimalarial researchers from around the world to collaborate on working towards the development of harmonised approaches for questioning participants about AE and non-study medication data. The results should now be taken forward for further refinement and pilot testing of harmonised tools. These will require deliberation about optimal permutations of items and the potential use of mobile phones, diaries and rating scales.

## **9. CONCLUSION**

The development of an accurate understanding of a drug's safety profile is essential for all medicines, especially for the antimalarials which are distributed widely to vulnerable at-risk populations, including uninfected persons as part of prevention strategies. The participant-reported data that contribute to drug safety assessments can be influenced by the elicitation methods used to collect this information. A harmonised approach for collecting AE and non-study medication data during uncomplicated malaria clinical studies could contribute to improving the interpretation, comparison and pooling of data from different studies. Such a harmonised approach could incorporate items that achieved consensus within this Delphi process for inclusion. For eliciting AEs these included: a general question concept, structured questions about certain symptoms, use of mobile phones, diaries, visual analogue scales and photographs of symptoms, and openly engaging with participants. For eliciting non-study medication reports, these include: a general question concept; structured questions about medicine sources, treatment classes and indications, and asking about

local treatments by name; showing photographs, drawings or samples of commonly used treatments, and asking participants to bring non-study medication to visits. One method of questioning may not be superior to another, or sufficient to fulfil its purpose on its own. As such, the results from this Delphi process suggest that combining questioning methods is optimal.

### **Competing interests**

There are no competing interests to declare.

### **Authors' contributions**

NM led data collection and analysis, contributed to the design of the study and wrote the paper. EA conceived of the study and assisted with the design, analysis and editing of the paper. CC and CP assisted with the design and KB had input throughout the research process.

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### **Declarations**

The data used to draw conclusions in this manuscript has been presented in this paper or has been included as additional supporting files submitted to the journal. Additional data containing participant-reported information can be made available once participants of the Delphi provide their consent.

**List of tables**

Table 2: Overall percentage of questions reaching consensus by sub-section.

Table 3: Summary of consensus status for individual questioning items.

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**PART D: APPENDICES**

**APPENDIX I: QUESTIONNAIRES**

*Questionnaires for rounds one, two and three of the Delphi*

**Round One Questionnaire****Working towards consensus on methods used to elicit, assess and record participant-reported adverse events data in uncomplicated malaria clinical drug trials/studies: A Delphi Process**

We are interested in harmonising how uncomplicated malaria clinical research participants (or their caregivers) are asked about health and treatment-taking to collect the following types of data: medical history, adverse events and previous or concomitant medications. This interest is driven by the fact that interpreting or synthesizing results is complicated if studies use different methods for ascertaining and assessing these data.

When answering the questions that follow please draw on your knowledge, experiences and opinions as well as the literature provided. Please be as candid as possible in order to add to the richness of our understanding of the different options.

\* The ACT Consortium is a group of researchers conducting projects relating to the implementation of Artemisinin-based combination therapies (ACT) for malaria treatment within Africa and Asia ([www.actconsortium.org](http://www.actconsortium.org)). This project is funded through a grant from the Bill & Melinda Gates Foundation to the London School of Hygiene & Tropical Medicine.

Ethical approval for this study was granted by the University of Cape Town Research Ethics Committee. If you have any concerns regarding your rights and welfare as they relate to this study you can contact the University of Cape Town Human Research Ethics Committee ([shuretta.thomas@uct.ac.za](mailto:shuretta.thomas@uct.ac.za) or on +27214066338).

**What will being part of this Delphi require from you?**

The aim of a Delphi process is to achieve consensus about a topic. In the first round we will present an overview of the methods used generally in clinical research, and more specifically in malaria clinical drug studies, to detect, assess and record participant-reported data used for assessing harms (adverse events and previous/concomitant medications). We will then ask participants to recommend any additional approaches to obtain these data (this may involve a repeat of some of our survey questions to ensure we capture all the relevant data, including information from Delphi panellists who did not take part in the survey).

In the second round you will be asked to rank the methods/approaches in terms of their relevance, importance and feasibility in uncomplicated malaria drug studies. In subsequent rounds we will send you a summary of the group's rankings, and where your own rankings fall. You will then be able to maintain your rankings or amend them. By the final round we hope to reach consensus between the panellists about which approaches, if any, are suitable for taking forward for testing and possible harmonisation within malaria clinical studies.

As a participant you may benefit from discussion with other malaria researchers with considerable experience and expertise in this field of research. A disadvantage is that a Delphi process can be time consuming and requires commitment to complete all rounds. We have, however, kept our questions as brief as possible while still ensuring richness of the data collected. It should take between 15 - 20 minutes to complete each round of the Delphi.

Once enrolled in the Delphi your identity will be concealed from other panellists and the study investigators (a research assistant not otherwise involved will manage communications). After the Delphi you are free to reveal your identity if you desire. We ask that you complete each round of the Delphi within two weeks of receiving the initial invitation. We strongly encourage you to complete all stages to add to the richness of the data collected and rigour of the study. If, however, you decide you no longer want to participate for any reason, you are free to withdraw at any point.

If you have not read the literature review yet you can do so by clicking the link below.

[Read literature review \(URL link\)](#)

If you have any queries please contact the study investigators Nyaradzo Mandimika (dzadz81@gmail.com) or Elizabeth Allen (elizabeth.allen@uct.ac.za).

If you would like to continue with the Delphi please enter your email address below and continue on to the next page. Please note that by continuing we will assume you have given consent to take part.

1. Please enter your email address below: \_\_\_\_\_

**Section A: How to ask participants about their health to collect adverse event data**

Through our previous survey we found that the following general question concepts are used to ask participants (or their caregivers) about their health to collect adverse events data:

- General question about feeling.  
(e.g. *'How have you [has your child] been feeling?'*)
- Explicit question about change in health.  
(e.g. *'Have you observed any change or new complaint since your last visit?'*)
- Question implying causality.  
(e.g. *'Did your child experience any side effects from the malaria treatment?'*)

2. Are there any other general question concepts that you consider as important and feasible for asking participants (or their caregivers) about health to collect adverse event data?

- Not applicable, I do not recommend general questions at all.
- No other general question concepts considered important.
- Yes (If yes, please describe)

**Section A: How to ask participants about their health to collect adverse event data**

In our previous survey people said that they use the following types of structured questions which offer participants (or their caregivers) options to pick from when asking about their health to collect adverse event data:

- Structured questions about malaria or non-malaria signs or symptoms, including possible expected adverse drug reactions. (e.g. *'Have you experienced fever, headache, skin rash?'* etc.)
- Structured questions about body parts, systems or functions. (e.g. *'Have you experienced a problem with your head, chest, heart, breathing?'* etc.)

For structured questions, the tools shared with us by survey participants include the following items:

**Signs or symptoms** (including possible adverse drug reactions):

Headache	Tinnitus
Fever	Hearing problem
Skin rash	Vision/sight problem
Pruritus	Palpitation
Cough	Change in urine colour
Anorexia	Fatigue
Muscle pain	Confusion
Weakness/Lethargy	Numbness
Vomiting	Sleep disturbance
Loss of appetite	Nightmares
Dizziness	<b>Infants:</b>
Behavioural change	Crying more than usual
Joint pain	Abnormal sucking
Abdominal pain	<b>Pregnant women:</b>
Allergic skin rash	Baby movements less than normal
Non-allergic skin rash	Contractions more than usual
Itching (no rash)	Vaginal bleeding
Diarrhoea	

**Body parts, systems or functions:**

Ears	Endocrine
Eyes	Lymphatic
Head	Cardiovascular
Chest	Respiratory/breathing
Nose	Neurological

3. Are there any other structured question items that you consider as important and feasible for asking participants (or their caregivers) about health to collect adverse event data?

- Not applicable, I do not recommend structured questions at all.
- No other structured question considered important.
- Additional signs or symptoms. (Please describe additional signs or symptoms)
- Additional body parts, systems or functions. (Please describe body parts, systems or functions)

**Section A: How to ask participants about their health to collect adverse event data**

Through our previous survey we found that questions aided by the use of pictures or pictorial diaries are used to ask participants (or their caregivers) about their health to collect adverse events data.

**For example:**

- Drawing of a body outline for participants to consider.
- Photograph of a rash.

4. Please provide us with specific details of the items that you recommend should be included on pictorial questioning tools or diaries about health, for example drawing of a body outline for participants to consider, photograph of a rash etc. (Please be as exhaustive as possible).

- Not applicable, I do not recommend the use of pictorial question tools at all.
- No other pictorial question tools considered important.
- Photograph, drawing or picture of signs and symptoms, body parts or whole body outline. (Please describe the photograph, drawing or picture and/or upload an example).

**Section B: How to ask about previous or concomitant medication**

In our previous survey we found that the following types of general question concepts are used to ask participants about their use of non-study medications to collect previous or concomitant medication data:

**General questions about the use of medications.****For example:**

- *‘Have you taken any medications in the past 2 weeks/since the last visit?’*

5. Are there any other general question concepts that you consider as important and feasible for asking participants (or their caregivers) about non-study medications to collect previous or concomitant medication data?

- Not applicable, I do not recommend general questions at all.
- No other general questions considered important.
- Yes (If yes, please describe).

**Section B: How to ask about previous or concomitant medication**

In our previous survey we found that the following types of structured questions are used to ask participants about their use of non-study medications to collect previous or concomitant medication data:

**Questions about sources of medicine:**

Health facility	Chemical sellers
Drug shop	Health worker
Pharmacy	Traditional healer

**Questions about treatment classes/specific indication:**

Pain killer  
Antibiotic  
Antimalarial  
Vitamins

**Questions about treatment name:**

Amoxicillin	Sulfadoxine/pyrimethamine (Fansidar)
Artemether/lumefantrine	Co-trimoxazole
Aspirin	Paracetamol
Amodiaquine	Quinine
Chloroquine	

6. Are there any other structured question items that you consider as important and feasible for asking participants (or their caregivers) about non-study treatments?

- Not applicable, I do not recommend structured questions at all.
- No other structured question items considered important.
- Additional sources of medicines. (Please state additional sources of medicines).
- Additional treatment classes/ specific indication. (Please state additional treatment classes/ specific indication).
- Additional treatment name. (Please state additional treatment name).

**Section B: How to ask about previous or concomitant medication**

Through our previous survey we found that pictorial question tools are used to ask participants about their use of non-study medications to collect previous or concomitant medication data. Examples of these tools include:

- Photographs or drawings of drugs or drug packets
- Pictures of traditional medicines
- Pictures of mosquitoes
- Samples of commonly used drug packets

7. Please provide us with details of the items that you recommend should be included in pictorial question tools or used as examples.

- Not applicable, I do not recommend the use of pictorial question tools at all.
- No other pictorial question tools considered important.

- Photographs, drawings or pictures (Please describe the photograph, drawing or picture and/or upload an example).

### **Section B: How to ask about previous or concomitant medication**

Apart from general, structured or pictorial question methods, are there any other questioning methods or approaches that you consider as important and feasible for asking participants (or their caregivers) about use of non-study medications to collect previous or concomitant medication data?

- Yes (If yes, please describe).
- No

### **Section C: Other approaches to ensure accurate health and non-study medication reports from participants**

Please consider the following approaches that may be beneficial in ensuring accurate reports:

A phrase aimed at overcoming potential barriers to reporting about health or use of non-study medications.

#### **For example:**

- *'I am interested to hear about everything even if you think it is not important.'*
- *'Do not worry about telling me about something (like using herbs), you will not get into trouble.'*

Guidance for trial staff in managing communications through another person.

#### **For example:**

- Training in when and how to include children in discussions about their health when a caregiver is present.
- Training in how to manage conversations through a translator.

8. Are there any other questioning approaches (other than those mentioned above) that you consider as important and feasible for asking participants (or their caregivers) about their health or use of non-study medications?

- Yes (If yes, please describe).
- No

#### **Thank you!**

Thank you for taking the time to participate in this Delphi process. We appreciate your insights into this important and complex topic. For more information on this project, or if you are interested in collaborating with our research team, please contact Liz Allen at the University of Cape Town, South Africa (elizabeth.allen@uct.ac.za) or Nyari Mandimika (dzadz81@gmail.com).

## Round Two Questionnaire

### **Working towards consensus on methods used to elicit, assess and record participant-reported adverse events data in uncomplicated malaria clinical drug trials/studies: A Delphi Process.**

Thank you for completing round one of the Delphi process. We would now like to invite you to complete the second round.

In round one you and twenty-five others taking part were asked about different ways to question participants (or their caregivers) in uncomplicated antimalarial treatment studies in order to collect adverse event and non-study drug use data. We now present you with the collated suggestions from round one so that you can rate each type of question in terms of its relevance, importance and feasibility. The aim of this Delphi process is to achieve consensus on a 'menu' of harmonized or standard types of core questions to be used in a variety of uncomplicated antimalarial treatment studies.

Please keep in mind the focus of this Delphi process is safety (not efficacy), and in particular participants' subjective responses to questions about adverse events and concomitant (non-study drug) medicines. The Delphi does not consider how severity or causality of adverse events are assessed, though this may be considered in future work.

The different types of questioning methods need not be mutually exclusive so you can recommend more than one type. In future we will ask about preferred combinations for a global harmonized set of tools for eliciting adverse event (AE) and concomitant medication data.

We would like to encourage you once again to complete this round of the Delphi to ensure the rigour of the study findings.

\* The ACT Consortium is a group of researchers conducting projects relating to the implementation of Artemisinin-based combination therapies (ACT) for malaria treatment within Africa and Asia ([www.actconsortium.org](http://www.actconsortium.org)). This project is funded through a grant from the Bill & Melinda Gates Foundation to the London School of Hygiene & Tropical Medicine. Ethical approval for this study was granted by the University of Cape Town Research Ethics Committee. If you have any concerns regarding your rights and welfare as they relate to this study you can contact the University of Cape Town Human Research Ethics Committee ([shuretta.thomas@uct.ac.za](mailto:shuretta.thomas@uct.ac.za) or on +27214066338).

1. Please enter your email address below:

### **Section A: Asking participants about adverse events (AEs) in uncomplicated malaria treatment studies**

Please rate the following types of **GENERAL QUESTIONS** to reflect to what extent you agree or disagree that each item is relevant and important and feasible for detecting participant-reported AE data.

Please note that the questions below are only examples of possible phrases, exact terminology may be context-specific.

Please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

2. General question about feeling (e.g. '*How have you [has your child] been feeling since your last visit/ in the past x days [trial-specific time scale]?*')

1	2	3	4	5	6	7	8	9
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3. Explicit question about change in health (e.g. '*Have you observed any change or new complaint since your last visit/ in the past x days [trial-specific time scale]?*')

1	2	3	4	5	6	7	8	9
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4. Question implying causality (e.g. '*Did your child experience any side effect from the drug since your last visit/ in the past x days [trial-specific time scale]?*')

1	2	3	4	5	6	7	8	9
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5. General question about past adverse reactions to treatments (e.g. '*Have you ever reacted badly to a drug or vaccine?*').

1	2	3	4	5	6	7	8	9
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6. General question about rating any change in health (e.g. '*How do you rate your state of health after taking the study medicine?*').

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

Please rate the following types of **STRUCTURED QUESTIONS** to reflect to what extent you agree or disagree that each item is relevant and important and feasible for detecting participant-reported AE data.

Please note that the questions below are only examples of possible phrases, exact terminology may be context-specific.

Please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

Questions about body parts, systems or functions (e.g. '*Have you experienced a problem with your head, chest, heart, breathing?*' etc.):

7. Ears

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

8. Nose

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

9. Throat

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

10. Eyes

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

11. Head

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

12. Chest

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

13. Endocrine system (e.g. diabetes, thyroid)

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

14. Heart

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

15. Lungs/Breathing

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

16. Lymphatic system

1	2	3	4	5	6	7	8	9
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17. Nervous system (e.g. seizures, migraines)

1	2	3	4	5	6	7	8	9
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**Structured questions about signs or symptoms, including possible expected adverse drug reactions (e.g. 'Have you experienced fever, headache, skin rash etc.?').**

Some of these may be listed several times in different ways [e.g. different types of skin rash plus a summary question about skin problems]. You can indicate your preference through your rating score for each one.

18. Headaches

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

19. Fever

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

20. Cough

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

21. Tiredness/ fatigue/ weakness/ lethargy

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

22. Muscle pain

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

23. Joint pain

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

24. Abdominal pain

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

25. Loss of appetite

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

26. Vomiting

1	2	3	4	5	6	7	8	9
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27. Nausea

1	2	3	4	5	6	7	8	9
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28. Diarrhoea

1	2	3	4	5	6	7	8	9
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29. Mood/ behavioural change

1	2	3	4	5	6	7	8	9
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30. Skin rash

1	2	3	4	5	6	7	8	9
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31. Non-allergic skin rash (e.g. scabies)

1	2	3	4	5	6	7	8	9
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32. Allergic skin rash (e.g. some forms of urticaria)

1	2	3	4	5	6	7	8	9
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33. Itching (no rash)

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

34. Peeling skin

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

35. Skin abnormalities

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

36. Dizziness

1	2	3	4	5	6	7	8	9
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37. Tinnitus (ringing in the ears)/ hearing problem

1	2	3	4	5	6	7	8	9
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38. Vision/sight problem

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

39. Change in urine colour

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

40. Palpitations

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

41. Confusion

1	2	3	4	5	6	7	8	9
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42. Sleep disturbance/ nightmares

1	2	3	4	5	6	7	8	9
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43. Jaundice/icterus

1	2	3	4	5	6	7	8	9
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44. Oculogyric crisis

1	2	3	4	5	6	7	8	9
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45. Posturing

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

46. Photosensitivity (sensitivity to light)

1	2	3	4	5	6	7	8	9
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47. Spontaneous bleeding

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

48. Involuntary movements (e.g. rigors/ convulsions/ seizures)

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

49. Constipation

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

50. Blisters (on skin or mucous membrane)

1	2	3	4	5	6	7	8	9
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51. Hallucinations

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

52. Wheezing/ difficulty breathing

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

53. Pallor

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

54. Change in walking (gait disturbance)

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**In studies involving young children**

55. Crying more than normal

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

56. Abnormal sucking (if breastfed)

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

57. Eating/drinking/ feeding less than normal

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

58. Irritable

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

59. Difficult to arouse

1	2	3	4	5	6	7	8	9
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**In studies involving pregnant women**

60. Increased uterine contractions (more than normal)

1	2	3	4	5	6	7	8	9
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61. Baby movements less than normal

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

62. Vaginal bleeding

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

63. What is the maximum number of symptoms the participants can be reliably asked about?

Please rate the following types of **PICTORIAL QUESTIONING TOOLS** to reflect to what extent you agree or disagree that each item is relevant and important and feasible for detecting participant-reported AE data.

Please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

***Using photographs, drawings or pictures of the following signs and symptoms:***

64. Headache

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

65. Fever

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

66. Loss of appetite

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

67. Diarrhoea

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

68. Skin rash

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

69. Mucous membrane blisters

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

70. Jaundice

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

71. Joint pain

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

72. Pruritus

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Using photographs, drawings or pictures of the following body parts:**

73. Respiratory system

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

74. Gastrointestinal tract

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

75. Central nervous system

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

76. Skin

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

77. Whole body outline (to mark or point to)

1	2	3	4	5	6	7	8	9
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### **Other items**

In round one you and other participants were asked if there were any other questioning methods or approaches considered relevant, important and feasible for asking participants about AEs apart from the general, structured or pictorial methods. The responses suggested as potentially useful depending on the context are listed below.

Please rate each response to reflect to what extent you agree or disagree that each item is relevant and important and feasible for detecting participant-reported AEs in uncomplicated malaria treatment studies.

Please use the rating scale below.

1 = strongly disagree, 5 = neutral, 9 = strongly agree

78. Collecting AE reports using mobile phones

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

79. Collecting AE reports using patient diaries

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

80. Collecting AE reports using group discussions.

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

81. Using flip charts, with a picture on one side for the participant and a written question for the investigator on the reverse side (to reduce investigator variability).

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

82. Using video footage on smartphones or tablets to show how some AEs which are difficult to depict on still images may manifest e.g. seizure activity.

1	2	3	4	5	6	7	8	9
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83. Keeping an archive of digital photographs of AEs

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

84. Using an archive of visual analogue scales from day 0 throughout all the follow-ups to measure potential AEs and any change in the occurrence of these events.

1	2	3	4	5	6	7	8	9
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85. Openly engaging participants to discuss any concerns they have

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Section B: Asking participants about previous or NON-STUDY (CONCOMITANT) MEDICATION in uncomplicated malaria treatment studies.**

Please rate the following types of **GENERAL QUESTIONS** to reflect the extent to which you agree or disagree that each item is relevant and important and feasible to collect non-study medication data.

Please note that the questions below are only examples of possible phrases, exact terminology may be context-specific.

Please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

86. General questions about the use of non-study medications (e.g. *'Have you taken any medications since your last visit/ in the past x days [trial-specific time scale]?'*).

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

Please rate the following types of **STRUCTURED QUESTIONS** to reflect the extent to which you agree or disagree that each item is relevant and important and feasible to collect non-study medication data.

Please note that the questions are only examples of possible phrases, exact terminology may be context-specific.

Please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

Structured questions about source of medicine (e.g. *'Have you received any medication from a traditional healer since you were last seen here?' etc.*)

87. Medicine obtained from another health facility

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

88. Medicine obtained from a drug shop, pharmacy, chemical seller, the market (or equivalent)

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

89. Medicine obtained from a traditional healer, informal doctor (or equivalent)

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

90. Medicines already available in the home (from previous treatment courses).

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

91. Medicine obtained from family and/or friends

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

92. Collecting and using naturally occurring herbs/remedies

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Structured questions about treatment class or specified indication (e.g. 'Have you taken an antibiotic, anything for malaria, vitamins?')**

93. Analgesics/ anti-inflammatory drugs

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

94. Antibiotics

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

95. Antihistamines

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

96. Antimalarial

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

97. Vitamins

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

98. Please rate the following statement to reflect the extent to which you feel it is relevant and important and feasible for collecting non-study medication data.

***“Participants should be asked about individual treatments by name according to what is known to be locally relevant?”***

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

Please rate the following types of **PICTORIAL AND/OR OTHER PHYSICAL TOOLS** [used for questioning participants about non-study (concomitant) medication] to reflect the extent to which you agree or disagree that each item is relevant and important and feasible to collect non-study medication data.

Please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

**The following pictorial questioning tools or physical samples:**

99. Showing photographs or drawings of commonly used drugs or drug packets

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

100. Showing samples of commonly used drugs or drug packets

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

101. Showing photographs or drawings of commonly used herbs/traditional remedies

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

102. Showing samples of commonly used herbs/ traditional remedies

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

103. Asking participants to bring any non-study medication they may have taken before and/or during the trial/study to scheduled visits for a physical inspection

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Thank You!**

Thank you for taking the time to participate in this Delphi process. We appreciate your insights into this important and complex topic. For more information on this project, or if you are interested in collaborating with our research team, please contact Liz Allen at the University of Cape Town, South Africa ([elizabeth.allen@uct.ac.za](mailto:elizabeth.allen@uct.ac.za)) or Nyari Mandimika ([dzadz81@gmail.com](mailto:dzadz81@gmail.com)).

## **Round Three Questionnaire**

### **Working towards consensus among malaria clinical researchers on methods used to elicit harms data in uncomplicated malaria clinical drug studies: A Delphi Process.**

Thank you for completing round two of the Delphi process. We would now like to invite you to complete the third round.

In round two you and others taking part were presented with the collated suggestions from round one so that you could rate each type of question in terms of its relevance, importance and feasibility. We now present you with the summary of all responses from round two, along with your individual response, and we ask that you re-evaluate your rating score taking into consideration the summary of responses from the other experts taking part. Please refer back to your individual responses from round two when completing this round. Your individual responses will be sent to you via email within twenty-four hours of receiving the invitation to complete the third round. If you have not received your individual responses yet please contact Faikah Salie (faikah.salie@uct.ac.za) and she will resend it to you.

For each item, we will ask you if you would like to change your rating score or maintain your original value. The aim of this Delphi process is to achieve consensus on a 'menu' of harmonized or standard types of core questions to be used in a variety of uncomplicated antimalarial treatment studies. The different types of questioning methods need not be mutually exclusive so you can recommend more than one type.

Please keep in mind the focus of this Delphi process is safety (not efficacy), and in particular participants' subjective responses to questions about adverse events and concomitant (non-study drug) medicines.

We would like to encourage you once again to complete this round of the Delphi to ensure the rigour of the study findings.

\* The ACT Consortium is a group of researchers conducting projects relating to the implementation of Artemisinin-based combination therapies (ACT) for malaria treatment within Africa and Asia ([www.actconsortium.org](http://www.actconsortium.org)). This project is funded through a grant from the Bill & Melinda Gates Foundation to the London School of Hygiene & Tropical Medicine.

Ethical approval for this study was granted by the University of Cape Town Research Ethics Committee. If you have any concerns regarding your rights and welfare as they relate to this study you can contact the University of Cape Town Human Research Ethics Committee (shuretta.thomas@uct.ac.za or on +27214066338).

1. Please enter your email address below:

**We achieved consensus on some of the items in round two and we present them below. You are not asked to rate these items.**

Consensus was reached on all of the items listed below. This means that the panel collectively rated these items as being relevant, important and feasible for questioning participants in uncomplicated malaria treatment studies about AEs and concomitant medication using the different types of questioning methods mentioned in the Delphi. We defined consensus as having no less than 70 % of panellist selecting options which are within the same three-point region (1 - 3, 4 - 6, 7 - 9) containing the median.

**Asking participants about adverse events (AEs) in uncomplicated malaria treatment studies using GENERAL QUESTIONS:**

- Using an explicit question about change in health (e.g. 'Have you observed any change or new complaint since your last visit/ in the past x days [trial-specific time scale]?')

**Asking participants about adverse events (signs and symptoms) using STRUCTURED QUESTIONS:**

**We achieved consensus on the following items:**

- Headache
- Fever
- Cough
- Loss of appetite
- Vomiting
- Nausea
- Diarrhoea
- Skin rash
- Itching (no rash)
- Peeling skin
- Tinnitus (ringing in the ears)/ hearing problem
- Sleep disturbance/ nightmares
- Involuntary movements (e.g. rigors/ convulsions/ seizures)
- Wheezing/ difficulty breathing

**In infants:**

- Eating/drinking/ feeding less than normal
- Difficult to arouse

**In pregnant women**

- For Increased uterine contractions (more than normal)

**Additional questioning methods or approaches for asking participants about AEs apart from the general, structured or pictorial methods:**

- Keeping an archive of digital photographs of AEs.

**Asking participants about previous or non-study (concomitant) medication in uncomplicated malaria treatment studies using GENERAL QUESTIONS:**

- General questions about the use of non-study medications (e.g. 'Have you taken any medications since your last visit/ in the past x days [trial-specific time scale]?').

**Asking participants about source of medicines in uncomplicated malaria treatment studies using STRUCTURED QUESTIONS.**

**We achieved consensus on the following sources of medicines:**

- Medicine obtained from another health facility
- Medicine obtained from a drug shop, pharmacy, chemical seller, the market (or equivalent)
- Medicine obtained from a traditional healer, informal doctor (or equivalent)
- Medicines already available in the home (from previous treatment courses).
- Collecting and using naturally occurring herbs/remedies

**Asking participants about ADVERSE EVENTS in uncomplicated malaria treatment studies**

Please state for each of the following types of GENERAL QUESTIONS previously asked of you, whether you would like to change your rating score. The summary of responses will be presented below each question.

If you choose to change your rating, please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

2. General question about feeling (e.g. '*How have you [has your child] been feeling since your last visit/ in the past x days [trial-specific time scale]?*')

**Summary of responses:**

Rating score	Percentage of respondents
1	6.3%
2	18.8%
3	6.3%
4	6.3%
5	12.5%
6	0.0%
7	12.5%
8	6.3%
9	31.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

3. Question implying causality (e.g. 'Did your child experience any side effect from the drug since your last visit/ in the past x days [trial-specific time scale]?')

**Summary responses:**

Rating score    Percentage of respondents

1	12.5%
2	6.3%
3	25.0%
4	6.3%
5	12.5%
6	6.3%
7	18.8%
8	0.0%
9	12.5%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

4. General question about past adverse reactions to treatments (e.g. 'Have you ever reacted badly to a drug or vaccine').

**Summary responses:**

Rating score    Percentage of respondents

1	18.8%
2	0.0%
3	6.3%
4	18.8%
5	6.3%
6	0.0%
7	6.3%
8	12.5%
9	31.3%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

5. General question about rating any change in health (e.g. 'How do you rate your state of health after taking the study medicine?').

**Summary responses:**

Rating score    Percentage of respondents

1	18.8%
2	0.0%
3	6.3%
4	12.5%
5	6.3%
6	12.5%
7	25.0%
8	18.8%
9	0.0%

Would you like to change your rating score? \*This question is required.

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

### Asking participants about ADVERSE EVENTS in uncomplicated malaria treatment studies

Please state for each of the following types of STRUCTURED QUESTIONS previously asked of you, whether you would like to change your rating score. The summary or responses will be presented below each question.

If you choose to change your rating, please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

Please note that the questions below are only examples of possible phrases, exact terminology may be context-specific.

### Questions about body parts, systems or functions (e.g. '*Have you experienced a problem with your head, chest, heart, breathing?*' etc.):

#### 6. Ears

##### Summary responses:

Rating score    Percentage of respondents

1	12.5%
2	6.3%
3	0.0%
4	0.0%
5	18.8%
6	18.8%
7	18.8%
8	6.3%
9	18.8%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 7. Nose

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	12.5%
3	0.0%
4	0.0%
5	18.8%
6	6.3%
7	25.0%
8	12.5%
9	18.8%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 8. Throat

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	12.5%
3	0.0 %
4	6.3%
5	12.5%
6	12.5%
7	18.8%
8	12.5%
9	18.8%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 9. Eyes

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	12.5%
3	0.0%
4	0.0%
5	18.8%
6	6.3%
7	25.0%
8	6.3%
9	25.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

#### 10. Head

##### Summary responses:

Rating score	Percentage of respondents
--------------	---------------------------

1	6.3%
2	6.3%
3	0.0%
4	0.0%
5	25.0%
6	6.3%
7	25.0%
8	12.5%
9	18.8%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

#### 11. Chest

##### Summary responses:

Rating score	Percentage of respondents
--------------	---------------------------

1	6.3%
2	6.3%
3	0.0%
4	0.0%
5	18.8%
6	12.5%
7	37.5%
8	6.3%
9	12.5%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

#### 12. Endocrine system (e.g. diabetes, thyroid)

##### Summary responses:

Rating score	Percentage of respondents
--------------	---------------------------

1	12.5%
2	12.5%
3	12.5%
4	0.0%
5	50.0%
6	0.0%
7	6.3%
8	0.0%
9	6.3%

Would you like to change your rating score?

- Yes
- No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

13. Heart

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	6.3%
3	6.3%
4	12.5%
5	18.8%
6	12.5%
7	25.0%
8	0.0%
9	12.5%

Would you like to change your rating score?

- Yes
- No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

14. Lungs/Breathing

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	0.0%
3	0.0%
4	0.0%
5	25.0%
6	12.5%
7	31.3%
8	12.5%
9	12.5%

Would you like to change your rating score?

- Yes
- No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 15. Lymphatic system

**Summary responses:**

Rating score    Percentage of respondents

1	18.8%
2	12.5%
3	12.5%
4	0.0%
5	37.5%
6	0.0%
7	12.5%
8	0.0%
9	6.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 16. Nervous system (e.g. seizures, migraines)

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	0.0%
3	6.3%
4	6.3%
5	12.5%
6	18.8%
7	18.8%
8	6.3%
9	25.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Asking participants about SIGNS OR SYMPTOMS (including possible expected adverse drug reactions) in uncomplicated malaria treatment studies**

Please state for each of the following types of **STRUCTURED QUESTIONS** about signs or symptoms (including adverse drug reactions) previously asked of you, whether you would like to change your rating score. The summary or responses will be presented below each question.

If you choose to change your rating, please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

## 17. Tiredness/ fatigue/ weakness/ lethargy

**Summary responses:**

Rating score	Percentage of respondents
1	12.5%
2	0.0%
3	0.0%
4	0.0%
5	6.3%
6	25.0%
7	0.0%
8	31.3%
9	25.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 18. Muscle pain

**Summary responses:**

Rating score	Percentage of respondents
1	12.5%
2	0.0%
3	0.0%
4	12.5%
5	12.5%
6	0.0%
7	0.0%
8	31.3%
9	31.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 19. Joint pain

**Summary responses:**

Rating score	Percentage of respondents
1	12.5%
2	0.0%
3	6.3%
4	0.0%
5	6.3%
6	12.5%
7	0.0%
8	31.3%
9	31.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

20. Abdominal pain

**Summary responses:**

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	0.0%
5	6.3%
6	18.8%
7	6.3%
8	18.8%
9	37.5%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

21. Mood/ behavioural change

**Summary responses:**

Rating score    Percentage of respondents

1	14.3%
2	0.0%
3	0.0%
4	0.0%
5	14.3%
6	14.3%
7	21.4%
8	21.4%
9	14.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 22. Non-allergic skin rash (e.g. scabies)

**Summary responses:**

Rating score	Percentage of respondents
1	25.0%
2	0.0%
3	12.5%
4	6.3%
5	12.5%
6	18.8%
7	12.5%
8	6.3%
9	6.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 23. Allergic skin rash (e.g. some forms of urticaria)

**Summary responses:**

Rating score	Percentage of respondents
1	25.0%
2	0.0%
3	0.0%
4	0.0%
5	6.3%
6	6.3%
7	18.8%
8	31.3%
9	12.5%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 24. Skin abnormalities

**Summary responses:**

Rating score	Percentage of respondents
1	12.5%
2	0.0%
3	0.0%
4	6.3%
5	12.5%
6	12.5%
7	18.8%
8	18.8%
9	18.8%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

### 25. Dizziness

#### Summary responses:

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	6.3%
4	0.0%
5	6.3%
6	6.3%
7	12.5%
8	25.0%
9	31.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

### 26. Vision/sight problem

#### Summary responses:

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	12.5%
4	0.0%
5	6.3%
6	6.3%
7	0.0%
8	25.0%
9	37.5%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

### 27. Change in urine colour

#### Summary responses:

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	0.0%
5	25.0%
6	6.3%
7	12.5%
8	18.8%
9	25.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

### 28. Palpitations

#### Summary responses:

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	6.3%
5	12.5%
6	6.3%
7	18.8%
8	25.0%
9	18.8%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

### 29. Confusion

#### Summary responses:

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	12.5%
5	6.3%
6	0.0%
7	25.0%
8	12.5%
9	31.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 30. Jaundice/icterus

**Summary responses:**

Rating score	Percentage of respondents
1	12.5%
2	0.0%
3	0.0%
4	6.3%
5	12.5%
6	6.3%
7	25.0%
8	25.0%
9	12.5%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 31. Oculogyric crisis

**Summary responses:**

Rating score	Percentage of respondents
1	12.5%
2	6.3%
3	12.5%
4	6.3%
5	18.8%
6	12.5%
7	18.8%
8	6.3%
9	6.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 32. Posturing

**Summary responses:**

Rating score	Percentage of respondents
1	12.5%
2	6.3%
3	6.3%
4	6.3%
5	18.8%
6	6.3%
7	31.3%
8	0.0%
9	12.5%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

33. Photosensitivity (sensitivity to light)

**Summary responses:**

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	6.3%
5	18.8%
6	0.0%
7	31.3%
8	12.5%
9	18.8%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

34. Spontaneous bleeding

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	0.0%
3	0.0%
4	0.0%
5	12.5%
6	18.8%
7	18.8%
8	12.5%
9	31.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

35. Constipation

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	0.0%
3	12.5%
4	0.0%
5	18.8%
6	6.3%
7	12.5%
8	18.8%
9	25.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

36. Blisters (on skin or mucous membrane)

**Summary responses:**

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	6.3%
5	6.3%
6	6.3%
7	18.8%
8	25.0%
9	25.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

37. Hallucinations

**Summary responses:**

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	0.0%
5	18.8%
6	12.5%
7	12.5%
8	25.0%
9	18.8%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 38. Pallor

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	6.3%
3	6.3%
4	0.0%
5	18.8%
6	18.8%
7	6.3%
8	18.8%
9	18.8%

Would you like to change your rating score?

 Yes No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 39. Change in walking (gait disturbance)

**Summary responses:**

Rating score    Percentage of respondents

1	13.3 %
2	0.0%
3	6.7%
4	0.0%
5	20.0%
6	13.3%
7	6.7%
8	20.0%
9	20.0%

Would you like to change your rating score?

 Yes No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**In studies involving young children**

## 40. Crying more than normal

**Summary responses:**

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	0.0%
5	18.8%
6	6.3%
7	12.5%
8	25.0%
9	25.0%

Would you like to change your rating score?

Yes No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

41. Abnormal sucking (if breastfed)

**Summary responses:**

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	0.0%
5	18.8%
6	6.3%
7	12.5%
8	12.5%
9	37.5%

Would you like to change your rating score?

 Yes No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

42. Irritable

**Summary responses:**

Rating score    Percentage of respondents

1	12.5%
2	6.3%
3	0.0%
4	0.0%
5	6.3%
6	6.3%
7	12.5%
8	31.3%
9	25.0%

Would you like to change your rating score?

 Yes No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**In studies involving pregnant women**

43. Baby movements less than normal

**Summary responses:**

Rating score    Percentage of respondents

1	12.5%
2	0.0%
3	0.0%
4	0.0%
5	12.5%
6	6.3%
7	12.5%
8	18.8%
9	37.5%

Would you like to change your rating score?

 Yes No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

44. Vaginal bleeding

**Summary responses:**

Rating score    Percentage of respondents

1	6.3%
2	0.0%
3	0.0%
4	0.0%
5	12.5%
6	12.5%
7	12.5%
8	12.5%
9	43.8%

Would you like to change your rating score?

 Yes No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Asking participants about ADVERSE EVENTS in uncomplicated malaria treatment studies**

Please state for each of the following types of **PICTORIAL QUESTIONING TOOLS** you were previously asked about, whether you would like to change your rating score. The summary or responses will be presented below each question.

If you choose to change your rating, please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

**Using photographs, drawings or pictures of the following signs and symptoms:**

45. Headache

**Summary responses:**

Rating score    Percentage of respondents

1	33.3%
2	6.7%
3	0.0%
4	13.3%
5	26.7%
6	0.0%
7	0.0%
8	20.0%
9	0.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

46. Fever

**Summary responses:**

Rating score    Percentage of respondents

1	26.7%
2	13.3%
3	0.0%
4	13.3%
5	20.0%
6	0.0%
7	13.3%
8	13.3%
9	0.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 47. Loss of appetite

**Summary responses:**

Rating score    Percentage of respondents

1	33.3%
2	6.7%
3	0.0%
4	13.3%
5	26.7%
6	0.0%
7	13.3%
8	6.7%
9	0.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 48. Diarrhoea

**Summary responses:**

Rating score    Percentage of respondents

1	2.0%
2	6.7%
3	0.0%
4	13.3%
5	20.0%
6	6.7%
7	6.7%
8	20.0%
9	6.7%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 49. Skin rash

**Summary responses:**

Rating score    Percentage of respondents

1	13.3%
2	6.7%
3	0.0%
4	0.0%
5	20.0%
6	6.7%
7	0.0%
8	26.7%
9	26.7%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

50. Mucous membrane blisters

**Summary responses:**

Rating score    Percentage of respondents

1	7.1%
2	7.1%
3	0.0%
4	0.0%
5	14.3%
6	7.1%
7	14.3%
8	21.4%
9	28.6%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

51. Jaundice

**Summary responses:**

Rating score    Percentage of respondents

1	0.0%
2	6.7%
3	6.7%
4	0.0%
5	26.7%
6	13.3%
7	13.3%
8	13.3%
9	20.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

52. Joint pain

**Summary responses:**

Rating score    Percentage of respondents

1	26.7%
2	13.3%
3	6.7%
4	0.0%
5	33.3%
6	0.0%
7	13.3%
8	6.7%
9	0.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

53. Pruritus

**Summary responses:**

Rating score    Percentage of respondents

1	20.0%
2	6.7%
3	13.3%
4	0.0%
5	33.3%
6	6.7 %
7	13.3%
8	6.7%
9	0.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Using photographs, drawings or pictures of the following body parts**

54. Respiratory system

**Summary responses:**

Rating score    Percentage of respondents

1	13.3%
2	6.7%
3	20.0%
4	6.7%
5	26.7%
6	6.7%
7	13.3%
8	0.0%
9	6.7%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

55. Gastrointestinal tract

**Summary responses:**

Rating score    Percentage of respondents

1	13.3%
2	6.7 %
3	20.0%

4	6.7%
5	26.7%
6	6.7%
7	6.7%
8	6.7%
9	6.7%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

#### 56. Central nervous system

##### Summary responses:

Rating score    Percentage of respondents

1	13.3%
2	20.0%
3	6.7%
4	13.3%
5	26.7%
6	0.0%
7	0.0%
8	6.7%
9	13.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

#### 57. Skin

##### Summary responses:

Rating score    Percentage of respondents

1	13.3%
2	6.7%
3	13.3%
4	0.0%
5	20.0%
6	0.0%
7	20.0%
8	0.0%
9	26.7%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

58. Whole body outline (to mark or point to)

**Summary responses:**

Rating score    Percentage of respondents

1	14.3%
2	0.0%
3	7.1%
4	7.1%
5	7.1%
6	7.1%
7	7.1%
8	21.4%
9	28.6%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Other items**

In round two you and other participants were asked to rate the additional methods or approaches suggested by some respondents as potentially useful (depending on the context), in terms of their relevance; importance and feasibility for asking participants about AEs apart from general; structured or pictorial methods or approaches.

Please state for each item below whether you would like to change your rating score. The summary or responses will be presented below each question.

If you choose to change your rating, please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

59. Collecting AE reports using mobile phones

**Summary responses:**

Rating score    Percentage of respondents

1	0.0%
2	0.0%
3	0.0%
4	6.7%
5	33.3%
6	6.7%
7	6.7%
8	26.7%
9	20.0%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 60. Collecting AE reports using patient diaries

**Summary responses:**

Rating score    Percentage of respondents

1	0.0%
2	0.0%
3	6.7%
4	13.3%
5	13.3%
6	6.7%
7	6.7%
8	20.0%
9	33.3%

Would you like to change your rating score?

 Yes No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 61. Collecting AE reports using group discussions

**Summary responses:**

Rating score    Percentage of respondents

1	13.3%
2	0.0%
3	13.3%
4	6.7%
5	26.7%
6	13.3%
7	6.7%
8	13.3%
9	6.7%

Would you like to change your rating score?

 Yes No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

62. Using flip charts, with a picture on one side for the participant and a written question for the investigator on the reverse side (to reduce investigator variability).

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	0.0%
3	6.7%
4	0.0%
5	46.7%
6	6.7%
7	13.3%
8	6.7%
9	13.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

63. Using video footage on smartphones or tablets to show how some AEs which are difficult to depict on still images may manifest e.g. seizure activity.

**Summary responses:**

Rating score    Percentage of respondents

1	0.0%
2	0.0%
3	0.0%
4	6.7%
5	33.3%
6	6.7%
7	13.3%
8	13.3%
9	26.7%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

64. Using an archive of visual analogue scales from day 0 throughout all the follow-ups to measure potential AEs and any change in the occurrence of these events.

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	0.0%
3	0.0%
4	0.0%
5	26.7%
6	20.0%
7	26.7%
8	13.3%
9	6.7%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

65. Openly engaging participants to discuss any concerns they have.

**Summary responses:**

Rating score    Percentage of respondents

1	7.1%
2	0.0%
3	0.0%
4	7.1%
5	21.4%
6	0.0%
7	21.4%
8	14.3%
9	28.6%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Asking participants about NON-STUDY MEDICATION in uncomplicated malaria treatment studies**

Please state for each of the following types of **STRUCTURED QUESTIONS** used to collect non-study medication data previously asked of you, whether you would like to change your rating score. The summary or responses will be presented below each question.

If you choose to change your rating, please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

Please note that the questions are only examples of possible phrases, exact terminology may be context-specific.

**Structured questions about source of medicine (e.g. 'Have you received any medication from a traditional healer since you were last seen here?' etc.)**

66. Medicine obtained from family and/or friends

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	0.0%
3	0.0%
4	0.0%
5	26.7%
6	0.0%
7	13.3%
8	20.0%
9	33.3%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Structured questions about treatment class or specified indication (e.g. 'Have you taken an antibiotic, anything for malaria, vitamins?')**

67. Analgesics/ anti-inflammatory drugs

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	13.3%
3	0.0%
4	0.0%
5	13.3%
6	13.3%
7	20.0%
8	13.3%
9	20.0%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

68. Antibiotics

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	6.7%
3	0.0%
4	0.0%
5	13.3%
6	6.7%
7	40.0%
8	13.3%
9	13.3%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 69. Antihistamines

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	13.3%
3	0.0%
4	0.0%
5	26.7%
6	13.3%
7	26.7%
8	13.3%
9	0.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 70. Antimalarial

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	6.7%
3	0.0%
4	0.0%
5	20.0%
6	6.7%
7	6.7%
8	20.0%
9	33.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

## 71. Vitamins

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	6.7%
3	6.7%
4	0.0%
5	33.3%
6	6.7%
7	13.3%
8	20.0%
9	6.7%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

72. Please rate the following statement to reflect the extent to which you feel it is relevant and important and feasible for collecting non-study medication data.

*“Participants should be asked about individual treatments by name according to what is known to be locally relevant.”*

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	0.0%
3	0.0%
4	0.0%
5	13.3%
6	13.3%
7	20.0%
8	20.0%
9	26.7%

Would you like to change your rating score?

Yes

No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Asking participants about in uncomplicated malaria treatment studies**

Please state for each of the following types of **PICTORIAL AND/OR OTHER PHYSICAL TOOLS** used for questioning participants about non-study (concomitant) medication previously asked of you, whether you would like to change your rating score. The summary or responses will be presented below each question.

If you choose to change your rating, please use the rating scale below in your assessment.

1 = strongly disagree, 5 = neutral, 9 = strongly agree.

**The following pictorial questioning tools or physical samples:**

73. Showing photographs or drawings of commonly used drugs or drug packets

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	0.0%
3	0.0%
4	0.0%
5	13.3%
6	13.3%
7	20.0%
8	13.3%
9	33.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

74. Showing samples of commonly used drugs or drug packets

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	0.0%
3	0.0%
4	0.0%
5	13.3%
6	13.3%
7	13.3%
8	33.3%
9	20.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

75. Showing photographs or drawings of commonly used herbs/traditional remedies

**Summary responses:**

Rating score    Percentage of respondents

1	6.7%
2	0.0%
3	0.0%
4	0.0%
5	13.3%
6	26.7%
7	20.0%
8	13.3%
9	20.0%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

76. Showing samples of commonly used herbs/ traditional remedies

**Summary responses:**

Rating score    Percentage of respondents

1	7.1%
2	0.0%
3	0.0%
4	0.0%
5	21.4%
6	14.3%
7	21.4%
8	21.4%
9	14.3%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

77. Asking participants to bring any non-study medication they may have taken before and/or during the trial/study to scheduled visits for a physical inspection

**Summary responses:**

Rating score    Percentage of respondents

1	14.3%
2	7.1%
3	0.0%
4	0.0%
5	14.3%
6	7.1%
7	21.4%
8	7.1%
9	28.6%

Would you like to change your rating score?

- Yes  
 No

If yes, please select your new rating score below:

1	2	3	4	5	6	7	8	9
---	---	---	---	---	---	---	---	---

**Thank You!**

Thank you for taking the time to participate in this Delphi process. We appreciate your insights into this important and complex topic.

For more information on this project, or if you are interested in collaborating with our research team, please contact Liz Allen at the University of Cape Town, South Africa (elizabeth.allen@uct.ac.za) or Nyari Mandimika (dzadz81@gmail.com).

**APPENDIX II: PARTICIPANT INFORMATION SHEET**

*Provided to participants in Round 1 of the Delphi*

**Working towards consensus on methods used to collect participant-reported harms-related data in uncomplicated malaria clinical drug trials/studies**

**What will be part of this Delphi require from you?**

The aim of Delphi is to achieve consensus about a topic. In the first round we will present an overview of the methods used generally in clinical research, and more specifically in malaria clinical drug studies, to detect, assess and record participant-reported data used for assessing harms (adverse events and previous/concomitant medications). Then we will ask participants to recommend any additional approaches to obtain these data (for those who took part in our survey, this may involve a repeat of some of those questions). In the second round you will be asked to rank the methods/approaches in terms of their relevance, importance and feasibility in uncomplicated malaria drug studies. In subsequent rounds we will send you a summary of the group's rankings, and where your own rankings fall. You will then be able to maintain your rankings or amend them. By the final (3rd of 4th) round we hope to reach consensus between the panellists about which approaches, if any, are suitable for taking forward for testing and possible harmonisation within malaria clinical studies.

As a participant you may benefit from discussion with other malaria researchers with considerable experience and expertise in this field of research. A disadvantage is that a Delphi can be time consuming and require commitment to complete all rounds. We have, however, kept our questions as brief as possible while still ensuring richness of the data collected.

Throughout the Delphi your identity will be concealed from other panellists and the study investigators (a research assistant not otherwise involved will manage communications). After the Delphi you are free to reveal your identity if desired. You have two weeks to submit responses to each round. We strongly encourage you to complete all stages to add to the richness of the data collected and rigour of the study. If for any reason you decide you no longer want to participate, however, you are free to withdraw at any point.

If you have any queries please contact the study investigators Ms Nyaradzo Mandimika (dzadz81@gmail.com) or Elizabeth Allen (elizabeth.allen@uct.ac.za). If you have any concerns regarding your rights and welfare as they relate to this study you can contact the University of Cape Town Human Research Ethics Committee (shuretta.thomas@uct.ac.za or on +27214066338).

If you would like to continue with the Delphi please [click here \[URL link\]](#). Please note that by following this link we will assume you have given consent to take part.

The ACT Consortium is a group of researchers conducting projects relating to the implementation of Artemisinin-based combination therapies (ACT) for malaria treatment within Africa and Asia ([www.actconsortium.org](http://www.actconsortium.org)).

**APPENDIX III: LITERATURE AND SURVEY RESULTS SUMMARY**

*Provided to participants in Round 1 of the Delphi*

**Working towards consensus on methods used to collect participant-reported harms-related data in uncomplicated malaria clinical drug trials/studies**

In order to discuss the merits and methods of harmonising the way we question antimalarial drug research participants to collect medical histories, adverse events and concomitant medication data, we have summarised some pertinent literature for prospective Delphi panellists, including our own work for this particular project.

The results of clinical research studies, syntheses of reports, and analyses of pooled individual participant harms data, are influenced by the methods used to collect such data. Different questioning methods about their health may elicit non-comparable responses from participants (Ioannidis *et al*, 2006). However, there is no consensus regarding the detail of how participants (in general or for malaria) should be questioned in order to generate medical history, adverse event (AEs) or previous/concomitant medication data. For AEs there is evidence that more detailed questioning (e.g. with reference to a checklist of possible symptoms or body functions) enhances responses (Bent *et al*, 2006; Greenhill *et al*, 2004). However, the effect of different question methods on the nature of reports is less clear. There are concerns that detailed methods could produce a deluge of ‘noise’, unhelpful AEs that cannot be distinguished from background rates, and that spontaneously reported events are either more clinically meaningful or more likely to be related to a trial drug compared to placebo (Barber & Santanello 1995; Wernicke *et al*, 2005).

There is a dearth of research about the way medical histories and previous/concomitant medications are elicited in clinical research, despite evidence that participants fail to report medication use when asked (Hodel *et al*, 2009). In other areas of

pharmacoepidemiology, including case-control or cohort studies and administrative databases, there has been methodological investigation regarding the accuracy of self-reported past medical conditions and medications, through comparison with medical or prescription records (West *et al*, 2005). In those contexts, recall of medical history appears dependent somewhat on the type of condition, its significance, and a willingness to share information. Pattern-of-use is influential in recall of past medications, and indication- or medication-specific questions increase prevalence estimates compared to open-ended questions (Gama *et al*, 2009).

In our own work we explored the process of participant-reported health and previous/concomitant data elicitation in malaria and HIV drug interaction trials in South Africa and Tanzania (Allen *et al*, 2013a). Reports obtained through different questioning types (a general enquiry, followed by checklists of possible health issues and medications, and finally an in-depth interview) were compared. We also qualitatively explored participants' experiences of illness and use of medications, and their reporting behaviour. There was an overall increase in the number of reports from general enquiry, through checklists, to in-depth interview. Using checklists and interviews appeared to facilitate recognition of health issues and medications used, and consideration of what to report. Information was sometimes not reported initially because participants either 'forgot', the event or medication had 'low significance to them', it was 'considered not relevant', or because of 'perceived negative consequences of reporting'. South African inpatient malaria negative/HIV positive volunteers exhibited a 'trial citizenship', working to achieve the researchers' goals, compared to Tanzanian malaria outpatients who sometimes deferred responsibility for identifying which items to report to the trial doctor. The different trial contexts thus appeared to cultivate some specific conditions that had a role in mediating recognition,

reporting and articulation of these important variables.

Participants in both sites overwhelmingly recommended that more detailed questioning (checklists or in-depth interviews) helped them to report. Investigators, meanwhile, spoke in their own focus group discussions of the challenge of eliciting comprehensive but relevant data when we will never know everything. For well-studied drugs, the focus of more detailed questioning could be on known or an anticipated risk, combined with general enquires to detect anything else. But it is a quandary whether to probe for AEs that are perhaps insignificant or irrelevant to both investigators and participants. There was, however, concern that selective detailed questioning could miss minor illness that impacts on adherence, and thus efficacy and an increased risk of malaria resistance at a population level. These clinicians, reflecting how patients may be intimidated by them despite them being at pains to be otherwise, suggested that other cadres of staff be involved to overcome barriers to reporting, whether in designing elicitation strategies (social scientists), questioning participants (nurses or social scientists) or interpreting safety results (anthropologists)

We propose, based on our own research, that some barriers to reporting may be overcome by using a checklist-type of method, while others may require a different approach (such as counselling participants to quell potential concerns about reporting). However, our work was limited to two clinical sites and therefore may not be generalizable. There may be a need for researchers to reflect on their own context when considering potential barriers to reporting and possible solutions in terms of questioning methods or approaches. To contribute to knowledge about this area we recently conducted a survey of antimalarial drug clinical researchers about the methods they used in their own studies (Allen *et al*, 2013b). In this, currently unpublished,

survey we included 52 responses from 25 counties; 87% working at an investigational site and 75% reporting about an interventional study. For AEs, questioning in 31% of interventional studies was a combination of general (e.g. open questions about health) and structured (e.g. reference to specific health-related items), 26% used structured only and 18% general only. No observational studies used general questioning alone. A minority of studies incorporated pictorial tools. Rationales for the questioning approach included: standardisation of assessment or data capture, specificity or comprehensiveness of data sought, avoiding suggesting a response, feasibility, and seeking to understand participants' perceptions. Most respondents considered the approach they reported as optimal, though several later reconsidered this. Combining general and structured questions about non-study drug use were considered useful for revealing and identifying specific medicines, while pictures were said to enhance reports, particularly in areas of low literacy.

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**APPENDIX IV: ETHICS APPROVAL LETTER**

*Letters of approval and renewal from the UCT Human Research Ethics Committee*

UNIVERSITY OF CAPE TOWN



Faculty of Health Sciences  
Faculty of Health Sciences Human Research Ethics Committee  
Room E52-24 Groote Schuur Hospital Old Main Building  
Observatory 7925  
Telephone [021] 406 6338 • Facsimile [021] 406 6411  
e-mail: [sumayah.ariefdien@uct.ac.za](mailto:sumayah.ariefdien@uct.ac.za)  
[www.health.uct.ac.za/research/humanethics/forms](http://www.health.uct.ac.za/research/humanethics/forms)

19 September 2013

HREC REF: 516/2013

Prof K Barnes  
Clinical Pharmacology  
K-Floor  
OMB

Dear Prof Barnes

**PROJECT TITLE: ACT PROJECT 16 EXTENSION: DEVELOPMENT OF HARMONISED APPROACHES FOR DETECTING AND RECORDING PARTICIPANT-REPORTED ANTIMALARIAL SAFETY DATA PART 3: DELPHI PROCESS**

Thank you for your letter dated 16 September 2013, addressing the issues raised by the Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has formally approved the above mentioned study.

Approval is granted for one year till the 30 September 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, HSF HUMAN ETHICS**

Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA),  
xArifidien



**FHS016: Annual Progress Report / Renewal**

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30/09/2015
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC		<b>Signed</b>	Date Signed 29/11/2014

Comments to PI from the HREC

**Signed**

Principal Investigator to complete the following:

**1. Protocol information**

Date (when submitting this form)	28 Nov 2014 (NB the slight delay in submission of this form was because it was unclear at that particular time whether the Delphi would be ongoing or draw to a close).		
HREC REF Number	516/2013	Current Ethics Approval was granted until	30 Sept 2014
Protocol title	ACT Project 16 Extension: Development of harmonised approaches for detecting and recording participant-reported antimalarial safety data. Part 3: Delphi process		
Protocol number (if applicable)	NA		
Are there any sub-studies linked to this study?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor KI Barnes		
Department / Office Internal Mail Address	K45 Old Main Building, Groote Schuur Hospital, Observatory 7925		
1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	
1.2 If the study receives US Federal funding, does the annual report require full committee approval?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	

**2. List of documentation for approval**

NA
----

**3. Protocol status (tick ✓)**

<input type="checkbox"/>	Open to enrolment
<input checked="" type="checkbox"/>	Closed to enrolment (tick ✓)
<input type="checkbox"/>	Research-related activities are ongoing
<input type="checkbox"/>	Research-related activities are complete, long-term follow-up only
<input checked="" type="checkbox"/>	Research-related activities are complete, data analysis only
<input type="checkbox"/>	Main study is complete but sub-study research-related activities are ongoing
<input type="checkbox"/>	Study is closed → Please submit a Study Closure Form (FHS010)

**4. Enrolment**

Number of participants enrolled to date	25
Number of participants enrolled, since last HREC Progress report (continuing review)	NA
Additional number of participants still required	0

**5. Refusals**

Total number of refusals (participants invited to join the study, but refused to take part)	NA
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**6. Cumulative summary of participants**

Total number of participants who provided consent	25
Number of participants determined to be ineligible (i.e. after screening)	NA
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	9
Number of participants withdrawn at participants' request (i.e. changed their mind)	16
Number of participants withdrawn by PI due to toxicity or adverse events	NA (Delphi)
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	NA (Delphi)
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	See below
Some participants did not complete all rounds (as is typical for Delphi) but all data from previous rounds is valuable for the results.	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below.	0

**APPENDIX V: JOURNAL SUBMISSION GUIDELINES**

*Malaria Journal*

*BioMed Central Journal*

## INSTRUCTIONS FOR AUTHORS



### Research Articles

[Submission process](#) | [Preparing main manuscript text](#) | [Preparing illustrations and figures](#) | [Preparing tables](#) | [Preparing additional files](#) | [Style and language](#)

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Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time; when users return to the site, they can carry on where they left off.

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During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal, to elaborate on any issues relating to our editorial policies in the '[About Malaria Journal](#)' page, and to declare any potential competing interests.

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- Rich text format (RTF)
- Portable document format (PDF)
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- DeVice Independent format (DVI)

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Manuscripts for Research Articles submitted to *Malaria Journal* should be divided into the following sections (in this order):

- [Title page](#)
- [Abstract](#)
- [Keywords](#)
- [Background](#)
- [Methods](#)
- [Results and discussion](#)
- [Conclusions](#)
- [List of abbreviations used](#) (if any)
- [Competing interests](#)
- [Authors' contributions](#)
- [Authors' information](#)
- [Acknowledgements](#)
- [Endnotes](#)
- [References](#)
- [Illustrations and figures](#) (if any)
- [Tables and captions](#)
- [Preparing additional files](#)

The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database ([EMBL](#)), DNA Data Bank of Japan ([DDBJ](#)), GenBank at the NCBI ([GenBank](#)), Protein Data Bank ([PDB](#)), Protein Information Resource ([PIR](#)) and the Swiss-Prot Protein Database ([Swiss-Prot](#)).

For reporting standards please see the information in the [About](#) section.

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The title page should:

- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided
- if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "acknowledgements" section in accordance with the instructions below. Please note that the individual names may not be included in the PubMed record at the time a published article is initially included in PubMed as it takes PubMed additional time to code this information.

### [Abstract](#)

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: **Background**, the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your research reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. **Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the [CONSORT extension for abstracts](#).

### [Keywords](#)

Three to ten keywords representing the main content of the article.

### [Background](#)

The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

### [Methods](#)

The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see ['About this journal'](#).

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### [Results and discussion](#)

The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

### [Conclusions](#)

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

### [List of abbreviations](#)

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

### [Competing interests](#)

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

When completing your declaration, please consider the following questions:

#### *Financial competing interests*

- In the past three years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary

from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.

- Do you have any other financial competing interests? If so, please specify.

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Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

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In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

According to [ICMJE guidelines](#), An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

All contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, a department chair who provided only general support, or those who contributed as part of a large collaboration group.

#### Authors' information

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

#### Acknowledgements

Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation

of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

If you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the "acknowledgements" section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.

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Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

### Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

### References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Please avoid excessive referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

Only articles, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited; unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE. Citations in the reference list should include all named authors, up to the first six before adding 'et al.'

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#### Examples of the *Malaria Journal* reference style

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Smith JJ. The world of science. *Am J Sci*. 1999; 36:234-5.

##### *Article within a journal (no page numbers)*

Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. *BMC Medicine*. 2013;11:63.

##### *Article within a journal by DOI*

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. *Dig J Mol Med*. 2000; doi:10.1007/s801090000086.

##### *Article within a journal supplement*

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. *Blood* 1979;59 Suppl 1:26-32.

##### *Book chapter, or an article within a book*

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. *International review of cytology*. London: Academic; 1980. p. 251-306.

##### *OnlineFirst chapter in a series (without a volume designation but with a DOI)*

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. *Top Curr Chem*. 2007. doi:10.1007/128\_2006\_108.

##### *Complete book, authored*

Blenkinsopp A, Paxton P. *Symptoms in the pharmacy: a guide to the management of common illness*. 3rd ed. Oxford: Blackwell Science; 1998.

##### *Online document*

Doe J. Title of subordinate document. In: *The dictionary of substances and their effects*. Royal Society of Chemistry. 1999. <http://www.rsc.org/dose/title of subordinate document>. Accessed 15 Jan 1999.

*Online database*

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998.  
<http://www.healthwise.org>. Accessed 21 Sept 1998.

*Supplementary material/private homepage*

Doe J. Title of supplementary material. 2000. <http://www.privatehomepage.com>.  
Accessed 22 Feb 2000.

*University site*

Doe, J: Title of preprint. <http://www.uni-heidelberg.de/mydata.html> (1999).  
Accessed 25 Dec 1999.

*FTP site*

Doe, J: Trivial HTTP, RFC2169. <ftp://ftp.isi.edu/in-notes/rfc2169.txt> (1999).  
Accessed 12 Nov 1999.

*Organization site*

ISSN International Centre: The ISSN register. <http://www.issn.org> (2006). Accessed  
20 Feb 2007.

*Dataset with persistent identifier*

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from  
sweet and grain sorghum (*Sorghum bicolor*). GigaScience Database. 2011.  
<http://dx.doi.org/10.5524/100012>.

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