Collection of participant-reported safety data in antimalarial trials v1.1

Guidance document (for comment)

WorldWide Antimalarial Resistance Network (WWARN)

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WorldWide Antimalarial Resistance Network (WWARN)
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1. Purpose

Optimal drug use depends on a comprehensive assessment of benefits and harms. While considerable work in many therapeutic areas has been devoted to ensuring valid, reliable and comparable measures of drug efficacy, equivalent work has not been undertaken for safety outcomes. One particularly under-studied area is the factors influencing participant-reported data for safety assessments (adverse events, medical histories, and prior/concomitant medicines). A better understanding of this will enhance the conduct and interpretation of the results of individual trials and meta-analyses. This document provides a summary of pertinent literature, including methodological research conducted by the authors within malaria, to guide antimalarial researchers in this topic.

2. Definitions

Adverse drug reaction (ADR)
In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.[1]

Adverse event (AE)
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[1]

Adverse event of special interest (AESI)
A noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious (e.g. hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. Such events should be described in protocols or protocol amendments, and instructions provided for investigators as to how and when they should be reported to the sponsor.[2]

Harm
The totality of possible adverse consequences of an intervention or therapy; they are the direct opposite of benefits, against which they must be compared.[3]

Patient reported outcome measure (PROM): Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.[4]

Tolerability
The degree to which overt adverse effects can be tolerated by the subject.[5] *NB there is no standard method for how this is measured and/or who makes the assessment.*

3. Background

Trials rely on the collection of adverse events (AEs) which are assessed on a case-by-case basis and/or by aggregate statistical synthesis as to which are likely to be adverse drug reactions (ADRs).[2,6] While serious ADRs are critical outcomes, less serious ADRs are important contributions to morbidity and can negatively impact adherence and treatment-seeking.[7] Drug selection may also particularly hinge on an adverse effect profile with minimal differences between efficacies.[8] However, the distinction between safety and tolerability is unclear and the latter may be used differently within trials (is it mild AEs, participant-reported symptoms, concerned with acceptability, or otherwise?).

AE data are derived from relatively objective measurements such as physical examinations, laboratory tests or other specialised assessments, and subjective participant reports. Such data should be comprehensive and accurate, as should be other variables contributing to AE interpretation, such as medical histories, and prior/concomitant medication use.[9]

It is largely acknowledged, however, that different ways of questioning participants will impact what is said about health and treatment use, but there are various opinions on the optimal method(s). Investigating this area is methodologically challenging due to multiple possible subjective end points and because health and illness can be viewed as social, psychological and cultural constructions as well as biological realities.[10,11,12] Medicines are also understood differently depending on the cultural context and underlying beliefs about potential benefits or harms.[13] The concept of validity of these data within trials may therefore be different to how health and medicine use is experienced and interpreted from alternative perspectives.

Reasons for recommending one questioning method over another to obtain AEs data from participants in trials tend to be either a preference for: a) open, general, non-leading enquiries (some postulate this will prevent suggesting an AE to a participant that is not real), or b) more specific enquiry methods (because they are seemed systematic, better able to be standardised, and will prompt under-reported AEs).[14,15,16] Over and above this there are different opinions about which method elicits information that is more meaningful from a clinical or patient perspective, which is superior at detecting differences in AEs between study arms, and whether methods are complementary.[17,18,19]

4. The impact of questioning methods on data obtained

A systematic review of 33 studies comparing an open general enquiry with checklist-type questions, rating scales or interviews found that more specific questioning led to more AEs, as expected.[20] This was consistent regardless of study design, population, or therapeutic area. A subset of 6 studies suggested that more severe, bothersome or otherwise clinically relevant AEs were reported with an initial open enquiry, while some less severe, bothersome or clinically relevant AEs were only reported with a subsequent specific enquiry. One study showed quite severe or debilitating AEs only detected by interview, and others did not find a difference in AEs between elicitation methods. No conclusions could be made about the impact of question method on the ability to detect a statistically significant difference between study arms. While the variety and low quality of methods limited the review, it found a risk for under-detection of AEs with more general elicitation methods, some of which may be important clinically or to patients. Acceptability of questioning methods was not explicitly assessed in most studies, though in one, while participants did not mind, investigators felt the more intensive questioning too detailed and long.[21]

5. Why participants report differently depending on the questioning method

Our own study included in the above review sought to understand from participants in antimalarial drug interaction trials why they reported medical histories, AEs and non-study medicines differently

when asked about health and treatment-use by different questioning methods.[22] They said checklists and semi-structured interviews helped them remember information forgotten when asked a more general question. Detailed questioning also signalled the need to report AEs or non-study medications they had not considered significant or relevant to themselves or the trial. An underlying finding was a belief that what participants report is less important than what a test (e.g. blood sample or other assessment) can contribute to information about their health (and sometimes treatment use).

In South African healthy HIV-infected participants, information about concomitant medicines (and therefore AEs) was sometimes withheld from the trial team in case it impacted their place in the trial. They also appeared to have the trial aims in mind when considering formulating a response. Conversely, Tanzanian participants (all with malaria, HIV positive or negative) could worry about reporting traditional medicines and were largely focused on their malaria rather than the trial. These barriers to reporting in both scenarios were not generally overcome by more specific questioning and were either expressed during interviews or focus groups as second-hand reports.

6. Regulatory requirements relating to elicitation of participant-reported safety variables

The US FDA, the EMA and others follow international guidelines that stipulate "methods used to make the measurements of the endpoints, both subjective and objective, should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness".[23] This suggests all harm-related endpoints, including participant-reported AEs, must adhere, which is not reflected in other guidelines, appears not to be done in practice, and may indeed be unworkable. The FDA notes that certain effects are unlikely to be readily reported without special attention, such as sexual dysfunction from antidepressants, in which case targeted safety questionnaires or validated instruments would be pertinent.[24] While there is no requirement to use a specific method for eliciting AEs, it is mandatory to be explicit about the method(s) in study reports.[6,25] This is reflected in the CONSORT Statement harms extension for reporting trials so that those evaluating safety data may take the methods into consideration, because of their potential impact on the trial results.[3]

7. Other guidance

A Council for International Organizations of Medical Sciences (CIOMS) working group report emphasises that dialogue about health to obtain AEs between participants and investigators has not received much attention and consider this to be "one of the most important issues that is rarely addressed".[2] They recommend processes should be consistent site to site, program to program, and clearly outlined in protocols, informed consent documents and in training. They recommend "it is probably best to frame questions to the patients in general terms rather than invoke the possibility that study treatment may be responsible for ill effects". Care should be taken to avoid leading questions. Furthermore, "although it is not advisable to read a specific list of possible ADRs when soliciting the patient's recent experience, patients should be alerted to known signs and symptoms indicative of medically important suspected or established ADRs in order to alert the investigator as early as possible". CIOMS goes beyond regulatory agency recommendations by advocating for specific enquiry of participants about use of herbal and other non-traditional medicines. They also mention the lack of regulatory guidance for the challenging task of gathering subjective data from young children and other scenarios where a proxy may need to be involved in a conversation about health.

8. Patient-reported outcome measures (PROMs)

While all participant-reported AE data are potentially measures of drug safety, the validated instruments mentioned above may include so-called PROMs.[4] However, when an instrument is used to elicit participant reports of AEs, it may not always be possible to present the data as frequencies

(unless for instance a score signifies incidence of a specific AE). Instead, the output may represent a concept about health presented without interpretation from a clinician. Data may still be submitted to authorities to support claims in medical product labelling provided they reliably measure the claimed concept in the population enrolled in the trial.[4] Such patient-reported outcome measures (PROMs) have traditionally been used for efficacy outcomes and their use for outcomes relating to harm is far less developed or understood, however there is work being done in this regard.[26,27]

9. What questioning methods are malaria researchers using?

For malaria efficacy trials, the WHO recommends that, to ascertain the incidence of AEs, participants be asked about symptoms that have emerged since the previous follow-up visit by "direct questioning", though the detail for how this should be done is not given.[28] We conducted an online survey with malaria trialists and found a range of methods used with overlapping rationales for choice and in various permutations to elicit AEs, medical history and non-study medication reports; 31% of interventional studies used a combination of general and structured questioning, 26% used structured only and 18% general only. A minority incorporated pictorial tools. It was not always clear how staff were using checklists, as a questioning tool or for data collection of items reported in response to general enquiries. This is an important distinction, as is whether symptom 'tick-lists' (which may be a combination of malaria symptoms and potential AEs) are analysed independent of traditional AE reports (with the corresponding details on severity, causality etc.) or if they are a means to completing AE data fields; ambiguity could impact individual participant data (IPD) analyses if it is not clear if the symptom and AE data contributed are duplications or independent.

10. What questioning methods could malaria researchers consider developing?

A mixed method study took a participatory approach to design novel forms for collecting AEs by non-clinicians in post-approval studies, focusing on the healthcare worker's perspective of participants' reporting behaviours and co-designing a pictorial storyboard to communicate the rationale for the information needed and facilitate rapport between the reporter and the respondent.[29] We conducted a modified Delphi technique study with a subset of the above survey participants who rated methods they considered relevant, important and feasible for collecting participant-reported AE and non-study medicines.[30] Consensus was achieved for a general question concept that did not imply causality (*e.g. 'Have you observed any change or new complaint since your last visit/ in the past x days [trial-specific time scale]?'*) and a check list enquiry of any of 39 signs/symptoms and 10 sources of medicines, treatment classes or specified indications that could be included in a trial-specific tool. Consensus was only reached for showing trial participants pictures or photos of two specific items to elicit reports: 'mucous membrane blisters' and 'skin rash'. Using mobile phones, patient diaries, rating scales and openly engaging with participants to discuss concerns were considered optimal complementary data-elicitation tools to develop, as have been used in low resource settings in other types of research and pharmacovigilance more widely. [31,32,33] It may be useful to design any pre-specific lists according to internationally recognised medical dictionaries, such as SNOMED (http://www.snomed.org/) and MedDRA (https://www.meddra.org/).

11. Recommendations

Based on the above findings the following recommendations are made for future discussion within the malaria research community:

- Ideally all those involved in collecting, managing and/or analysing trial safety data should understand the rationale for the method of eliciting participant reports and apply it in a standard manner as much as possible

- It is important to differentiate between checklists used to question participants about their health from those that capture what participants report in response to general, open enquiries
- Leading questions are inadvisable (i.e. "*don't you have x, y, z*?"), however, it is unclear whether asking participants to indicate which symptom they experienced from a list of options in a neutral non-leading manner has a nocebo effect
- Linking questions about health with those about medicines is intuitive (e.g. if someone reports a headache, "*did you use/take something for that?*")
- There should be a defined method for how items recorded on a day to day 'tick-list' are then recorded as AEs, and clarity about if such items are analysed independent of, or complementary to, traditional AEs in datasets contributed to those doing IPD meta-analyses
- Malaria research communities of practice could work towards harmonising how safety data are collected, assessed and reported, and consider co-developing novel questioning methods or tools based on methodological work
    - Common elements could be based on expected drug effects to strengthen interpretation, comparisons and meta-analyses of data from multiple similar trials
    - Extensive questioning may be unacceptable because of the high turnover of patients; using a question filter approach may make a tool more efficient, and it may be useful for pre-specific lists to reflect internationally recognised medical dictionaries
    - Participants could be involved in developing simple messages to clarify the rationale for information they are being asked about, and to highlight that their experiences of health and treatments are as important as results from tests and examinations
    - Staff could be made aware of potential underlying structural barriers to reporting in the local context and helped to develop ways of overcoming them
    - Much could be learnt from PROMs as they use qualitative methods to understand and represent participants' subjective viewpoints while allowing for harmonisation in the way information is elicited
- There should be enough detail in trial reports and publications (or in supplementary material) so that readers understand the detail of the method use to elicit AE data. See the CONSORT website for the Harms extension guidance
- It would also be helpful to distinguish between how safety and tolerability were defined and measured, if applicable

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