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EDITORIAL

STARTER checklist for antimalarial therapeutic efficacy reporting

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Efficacious antimalarials are a cornerstone of the global effort to control and eliminate malaria. However, the spread of drug resistance threatens gains achieved over the early years of this century. Of particular concern is widespread artemisinin resistance in Southeast Asia and its recent emergence in Africa, threatening the efficacy of artemisinin-based combination therapies that currently offer our best treatments for malaria [1]. Prompt identification of the emergence and spread of antimalarial drug resistance is crucial to guarantee effective case management. At a country level, efficacy data are used by ministries of health and their partners to determine national treatment guidelines. Because parasites do not respect political and administrative boundaries, coordination of surveillance and control strategies at the regional and global level is necessary to guide larger containment strategies.

Since the 1960s, the foundation of antimalarial drug efficacy monitoring has been the use of therapeutic efficacy studies that monitor parasitological and clinical response in patients treated for malaria. Standardized methods for performance and analysis of these studies are codified in World Health Organization (WHO) guidance documents [2–4]. Despite the standardized guidance, recent investigation has identified frequent non-adherence to the WHO guidelines [1, 5]. Notably,

deviations from the standard of practice methodology are common, particularly related to analysis of genotyping data and definition of primary outcome indicators, and critical methodological details are often omitted from publications reporting efficacy data. As a consequence, there is the risk that reported efficacy could either be underestimated or overestimated, with readers not able to determine both the scope and the direction of the under- or overestimates. Such a loss in accuracy can obstruct the global effort to prevent and contain antimalarial drug resistance.

Incorporating comments from the WHO Global Malaria Programme, the Malaria Branch of the Centers for Disease Control and Prevention, the US President's Malaria Initiative, and the editors-in-chief and antimalarial efficacy section leads from the *American Journal of Tropical Medicine and Hygiene* and *Malaria Journal,* we have developed the Standardized Antimalarial Therapeutic Efficacy Reporting (STARTER) Checklist, which lays out best practices for reporting results of antimalarial efficacy studies. Similar to other reporting checklists, it has been registered and is available at the EQUATOR Network repository [6] (Table 1).

We emphasize that checklists are not replacements for peer-review [7], but rather tools to promote uniformity in reporting. Filling out the checklist does not substitute for careful adherence to the global WHO standards for efficacy trials. Efficacy trial investigators and sponsors that follow WHO's guidance and verify their adherence at the protocol development, implementation, analysis,

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Table 1 Standardized antimalarial therapeutic efficacy reporting (STARTER)

Section	Item no.	Recommendation
Introduction	1	(a) Describe current policy for the treatment of malaria
Study design and data collection methods		
Summary	2	(a) Provide dates and location(s) of study. For locations, include details at the district and city/village level, if available
		(b) Specify target sample size and power calculation
		(c) Define arms by site and drug
		(d) Describe any randomization or blinding procedures
Antimalarial studied and dosing specifics	3	(a) Specify antimalarial manufacturer
		(b) Describe source of medicine and/or quality control measures
		(c) Provide age or weight bands used for dosing
		(d) State whether doses were given with or without food
		(e) State timing of doses and whether all doses (or which doses) were directly observed
Inclusion and exclusion criteria	4	(a) Provide age range
		(b) Specify how fever (or history of fever) was measured and defined
		(c) Present parasite density range for inclusion (if any)
		(d) Specify minimum acceptable hemoglobin value (if any)
Patient follow-up	5	(a) List days participants were followed up and approximate time windows
		(b) Specify treatment of patients in the case of early or late treatment failure
		(c) Describe clinical and laboratory assessments performed at each follow-up visit
Outcome definition	6	(a) Define early and late treatment failure
		(b) Define adequate clinical and parasitological response
		(c) Specify primary efficacy indicator and how it was calculated
		(d) State how new infections, loss to follow-up, protocol violation, and indeterminate results were figured in primary efficacy calculations (e.g., censored, excluded)
Laboratory methods		
Microscopy	7	(a) State how slides were prepared
		(b) State how many microscopists read each slide
		(c) State how discrepancies were defined and resolved
		(d) State how parasite density was calculated
Molecular correction (recrudescence vs new infection)	8	(a) Specify markers used for genotyping
		(b) State whether all markers were assessed for all samples
		(c) Describe criteria used to determine new infection vs recrudescence, including both the definition of a match at each marker and the overall definition of recrudescence considering all markers
		For fragment-length polymorphic markers (e.g., *msp1*, *msp2*, microsatellites)
		(d) Specify range of fragment size differences that qualified as a match for each marker
		(e) Provide cut-off settings for PCR artefacts and stutter peaks
		(f) State how fragment lengths were measured (e.g., capillary electrophoresis or gel)
		For non-fragment-length polymorphic markers (e.g., SNP-barcodes, amplicon sequencing)
		(g) Describe sequencing methodology
		(h) Provide sequencing depth and cut-offs
		(i) Cite bioinformatics software and workflow
Data and results		
Patients reaching study outcomes	9	(a) Provide number of participants enrolled, lost to follow-up, withdrawn, and excluded
		(b) State reasons for exclusion
Participant composition by arm	10	Describe age, sex, initial parasite density, and initial hemoglobin

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Table 1 (continued)

Section	Item no.	Recommendation
Outcome by arm	11	(a) Provide % slide positivity amongst patients seen on Day 3 (with Day 0 defined as first day of treatment)
		(b) List number of late treatment failures classified as new infections, recrudescences, or indeterminate
		(c) List number of participants with adequate clinical and parasitological response
		(d) Report day 28 results for arms with follow up $\geq$ 28 days
		(e) Report day 42 results for all arms with follow up $\geq$ 42 days
		(f) Provide Kaplan–Meier estimates of efficacy, where new infections and cases with loss to follow up are censored
		(g) Provide estimates and confidence intervals of both uncorrected and PCR-corrected results
		(h) Disaggregate all outcomes by study arm (site, drug, and species)
		(i) Only calculate p-values if study was specifically designed and powered to detect a difference between arms
Genotyping data	12	Provide table or supplementary table of paired full genotyping data (observed alleles at each locus) and classification for each late treatment failure

Essential items to be included in reports of therapeutic efficacy of antimalarials for uncomplicated malaria

Please refer to WHO guidance for antimalarial efficacy monitoring, molecular techniques, and distinguishing reinfection from recrudescence after therapy [2–4]. Commonly found errors in therapeutic efficacy reports have been characterized recently [1, 5].

and reporting stages will likely find the STARTER checklist facilitates their manuscript development.

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Competing interests
The authors declare that they have no competing interests.

Author contributions
MMP and ESH drafted the initial version of the checklist and accompanying commentary. EAA, QB, MV and PJR reviewed and provided feedback and changes to the checklist and commentary. All authors read and approved the final manuscript.

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