Can approaches for collecting participant-reported harms in malaria clinical drug trials be harmonised?

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Adverse events: the more you search, the more you find

Ioannidis et al. *Ann Intern Med* 2006

Patients given a checklist of 53 possible adverse events reported 20-fold more than those who answered open-ended questions

Forgot

Confused by question

WHY?

Cultural issues

Is there more data ? Which data are valid? Does it matter?

Bent et al. Brief Communication: Better Ways To Question Patients about Adverse Medical Events: A Randomized, Controlled Trial. *Ann Intern Med*. 2006

ACTc sub-studies

Mixed method study nested in 2 similar ACTc trials

- Identify factors shaping reports of medical history, adverse events, non-study meds by participants enrolled in ARV/AM trials
- Inform practices for improving reporting in these contexts

Global survey of malaria trialists

- Explore how these data are obtained

Delphi study

- Consensus on the appropriate methods and/or tools to use

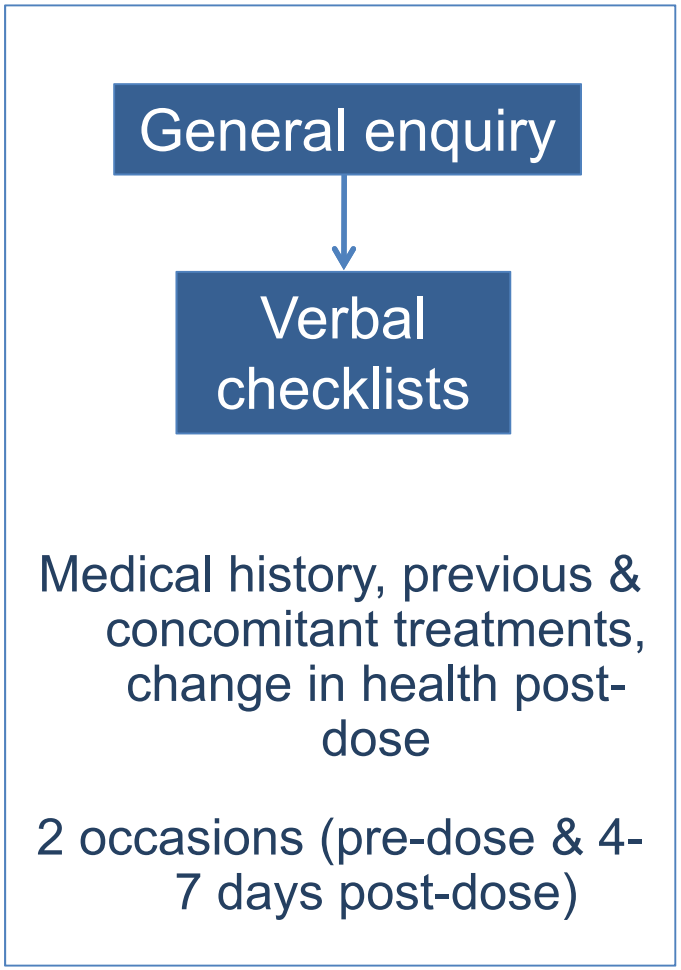
Mixed-method study

South Africa (n=18)
- In/out-patient
- HIV+/ARV+/malaria-

Tanzania (n=80)
- Out-patient
- Combinations of HIV+/ARV+/malaria±

Coartem® twice daily x 3 days

In-depth interviews/FGDs with those reporting differently between general enquiry/checklist
- Narrative
- Explanation



Mixed-method study cont.

Results

Overall increase in reports from general enquiry, through checklists, to in-depth interview

	South Africa			Tanzania		
	Medical histories	Adverse events	Meds	Medical histories	Adverse events	Meds
Number of reports by general enquiry*	4	23	17	285	6	196
Additional number of reports by checklists (% change from general enquiry)*	8 (200.0)	20 (87.0)	23 (135.3)	245 (86.0)	1 (16.7)	2 (91.3)
Additional number of reports by interview **(% change from general enquiry and checklist)	4 (33.3)	1 (2.3)	4 (10.0)	15 (2.8)	0 (0)	9 (4.5)

* All participants in the sampling frame attending both visits (South Africa n=16, Tanzania n=76)
**Subset of participants who took part in in-depth interviews (South Africa n=11, Tanzania n=16)

Checklists facilitated recognition of health issues/meds, & consideration of what to report. But did not overcome all barriers ……..

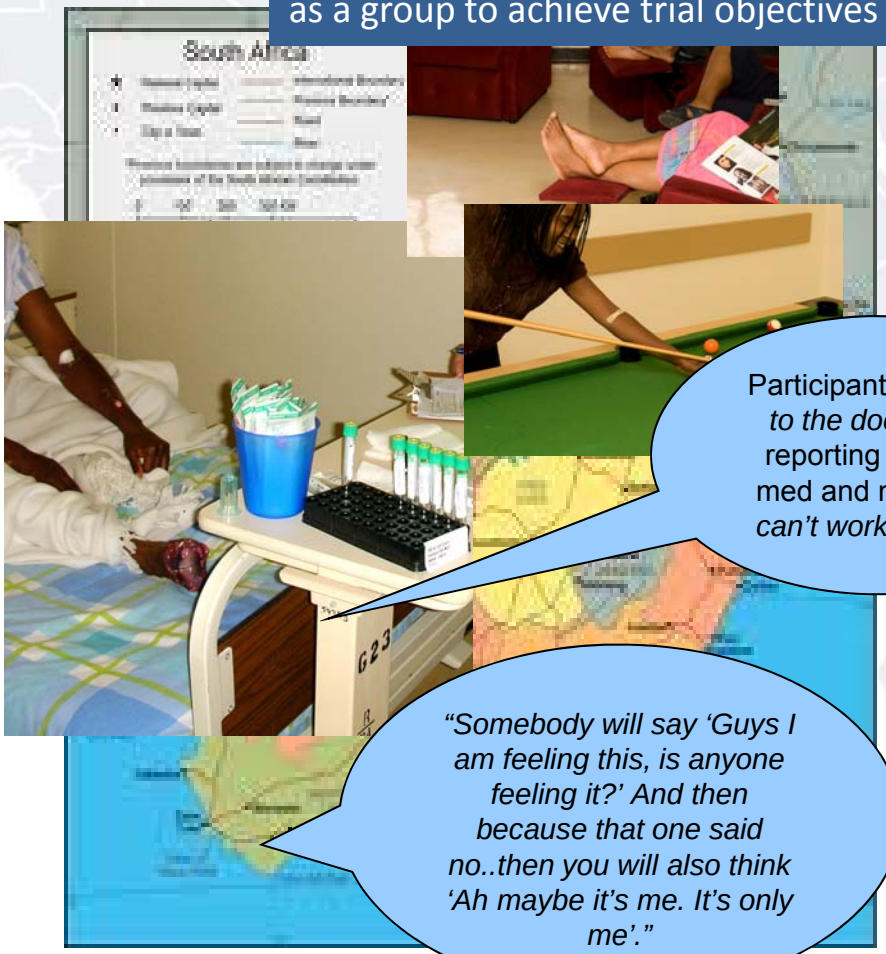
Certain information not reported initially as participants **forgot** or they had **low significance** (normalised, gauged against other experiences)

Information could be **not relevant** (*South Africa: trial-related, Tanzania: illness-related*), or have **negative consequences** (*South Africa: withdrawal from trial, Tanzania: against hospital 'rules'*)

Narratives suggested **inability to name** medicines, **questions inferior to blood tests**

Trial citizen or deferred responsibility?

Healthy in-patients working together as a group to achieve trial objectives



"I didn't forget or wasn't careless, but it's my knowledge that is low. A doctor knows that the head is aching so the eyes are also aching..The doctor adds "Aren't the eyes aching?"

Sick, outpatients accessing normal clinical care

Participant was *"fair to the doctor"* for reporting another med and now *"she can't work with us"*

"I was told I had malaria, so …they gave me some medicine ..The next day I came again to the hospital. And when I finished the dose I started feeling my head becoming normal"

"Somebody will say 'Guys I am feeling this, is anyone feeling it?' And then because that one said no..then you will also think 'Ah maybe it's me. It's only me'."

Mixed-method study cont.

Questioning methods/trial contexts influence detection of participant-reported safety data

Limitation to assessments and pooling of data

For exploration:

- Explain that checklists, if used, are examples, answers as important as tests
- Counsel against perceived punishment for non-reporting
- Find optimal phraseology
- Harmonisation?

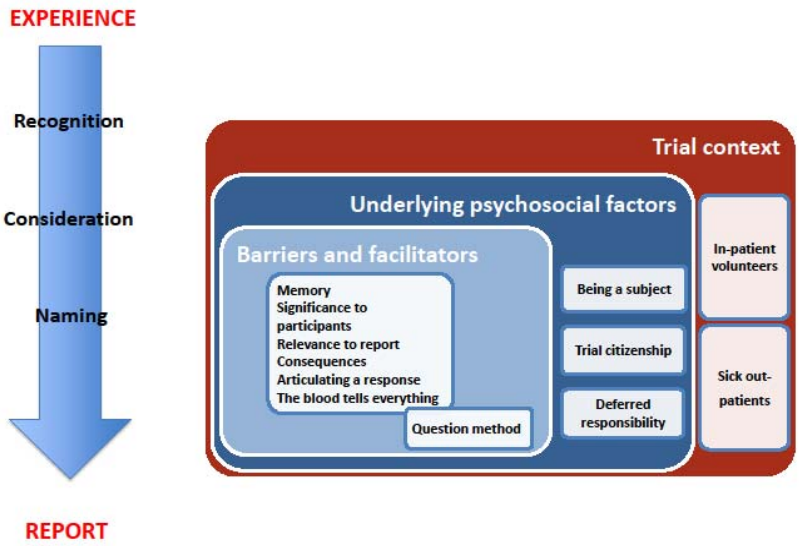


Figure 1: Diagram of trial participants' narrative responses

Online survey of malaria trialists

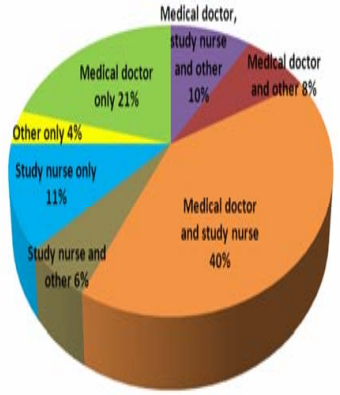
- E-mails, newsletters, flyers
- To capture detail, rationale and application of methods within various study designs and populations (last study conducted)
- Closed responses analysed by proportions, open responses by repeating ideas and underlying concepts

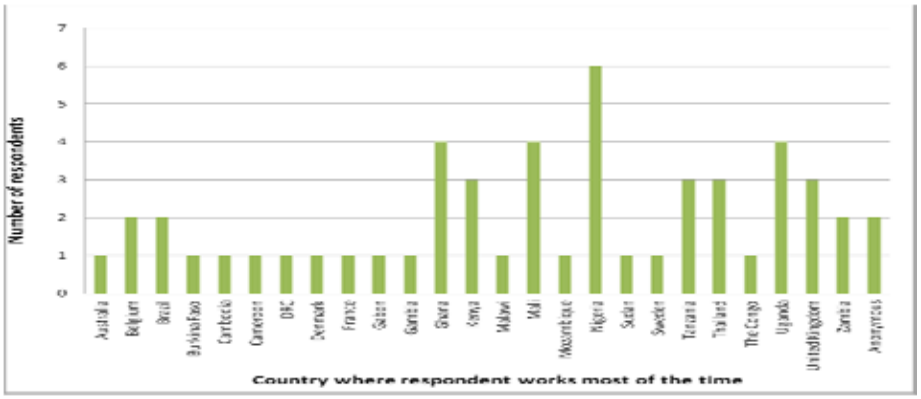
A snapshot, and sensitisation of a community of researchers for future discussions (Delphi)

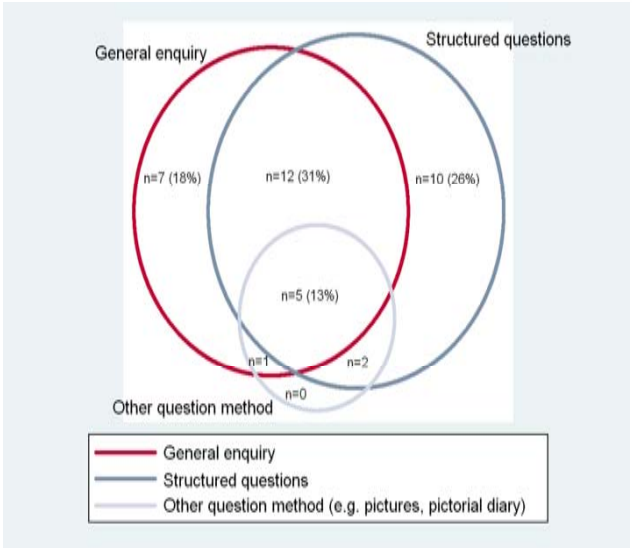
Survey cont.

Results

- 52 respondents from 25 countries, 87% at investigational site, 75% reporting about intervention study
- Interventional studies - 31% general/structured combination (open and specific questions), 18% general only, 26% structured only
- A minority incorporated pictorial tools







Rationale for questioning method (n=28)	Example quotes from survey respondents	Question method used in the study			
		General enquiry only	Structured enquiry only	General & structured enquiry combined	Addition of other tools*
Standardization of assessments or data capture (including historical use of a method in the research group)	*"A systematic approach based on pharmacovigilance procedures developed by our collaborators"* *"We are used to that"*	x	x	x	
Specificity of data sought (seeking information about particular adverse events, malaria symptoms or drugs)	*"We wanted to find out about specific symptoms and adverse effects"* *"The named drug questions targeted drugs of special interest"*	x	x	x	
Comprehensiveness of data sought (participant guidance, report clarification, overcoming barriers to reporting such as poor recall or ability to name medicines)	*"To provide a clear understanding about what investigators are looking for and to be sure they capture all complaints from study participants"* *"To get more information which may have been missed during the initial interview"*		x	x	x
Avoidance of suggestion	*"Keeping questions open and not leading so that only events significant to the patient are reported"*	x		x	
Feasibility	*"A simple screen [as the] main focus of the study was not safety/tolerability"* *"Appears simple and not complex"*	x	x	x	
Understand participants' perceptions about health	*"[To] know if [symptoms] are related to chronic disease or traditional belief"*		x	x	

Survey cont.

Results cont.

- Range of methods
- Overlap in use of different questioning methods to fulfill same rationale
- Most respondents considered approach they used as optimal, though several reconsidered this during the survey (on reflection?)
- 5 felt methods should depend on study design

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Delphi study ongoing

- Present summary results & relevant literature
- Suggest then rate questioning methods ito importance/feasibility
- Revise opinion if deviate from group

Potentially a basket of options for use/testing

Is there more data ? Which data are valid? Does it matter?

- Complex field (designs/contexts, triadic communications, validation)
- Cost of formative/technical work
- Sensitivity more important where risk:benefit & impact on adherence are greater
- Important to describe methods used in publications
- Questions unlikely to be “exhaustive and feasible”
- User-friendly data collection tools/databases

Thank you!

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