

# Challenges in eliciting safety data from trial participants

Allen E<sup>1</sup>, Barnes KI<sup>1</sup>, Mushi AK<sup>2</sup>, Massawe I<sup>2</sup>, Staedke SG<sup>3</sup>, Mehta U<sup>4</sup>, Vestergaard LS<sup>6</sup>, Lemnge MM<sup>2</sup>, Chandler CIR<sup>3</sup>

<sup>1</sup>University of Cape Town, South Africa, <sup>2</sup>National Institute of Medical Research, Tanzania, <sup>3</sup>London School of Hygiene and Tropical Medicine, UK <sup>4</sup>Independent Consultant, South Africa <sup>5</sup>University of Copenhagen, Denmark

# 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

Confused by question

Forgot

**WHY?**

Cultural issues

Is there more?

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



[www.actconsortium.com](http://www.actconsortium.com)

Anti-malarial/antiretroviral  
interaction trials (PK/PD)

### **-South Africa**

(in/out-patient, HIV+/ARV+/**malaria-**)

### **-Tanzania**

(out-patient, combinations of  
HIV+/ARV+/malaria $\pm$ )

Coartem<sup>®</sup> twice daily x 3 days

General enquiry



Checklist

Medical history, previous  
& concomitant  
treatments, change in  
health post-dose

2 occasions (pre-dose & 4-  
7 days post-Day 0)

# In-depth interviews & focus group discussions



## Selection criteria

Those reporting differently between general enquiry/checklist

- Narrative

- Explanation

A screenshot of the NVivo software interface. The main window displays a tree structure of nodes under the heading 'Tree Nodes'. The nodes are organized hierarchically, starting with 'ACT Pr 16', followed by 'InterACT', 'Seacat', and '01 Facilitators and barriers to reporting'. Under '01 Facilitators and barriers to reporting', there are five sub-nodes: '01 Memory', '02 Significance (NB no explicit reference to CL overcoming barrier)', '03 Relevance, misunderstanding', '04 Awareness of consequences', and '05 The trial was less about me personally that the researchers aims, I am a trial citizen'. The '05' node is expanded, showing a list of text excerpts. The right-hand pane displays a selected text excerpt, which is a conversation between EA and O5. The text discusses the challenges of reporting adverse events (AEs) during a trial, mentioning factors like time, pressure, and the desire to complete the trial. The text is as follows:

there wasn't going to be any [no: solution] solution so you didn't mention it. Um, and another thing that when I spoke to you that you mentioned to me now is this running tummy which goes on and off, on and off, you think it's due to food and diet. And also you didn't mention that to the doctor [O5: no I didn't], can you tell me the reason why maybe you didn't mention that? I am just interested in finding out.

O5: The thing is, as one of this research you have to write everything that happens to you by the end of the day. But the things that you come with to the research, those things I believe there are not really things that have to be put on the research because it end up giving the wrong information to this research. [EA: okay] so that's why I didn't mention it because I think this is the thing that I can actually. Like if I think of drinks like the sparkling fruit juice I drink these but I know by the end of the day it will make my tummy loose [EA: oh okay] So if I am to say 'my tummy is loose because I was here' and then it won't be part, this is actually not part of the...

EA: Not part of the trial? [O5: umm]. Ok, do you, ummm think it will interfere with the trial in some way?

O5: No it won't. [EA: okay] But once, if I mention it then it will be interfering because it won't be not what's...

EA: Interfering with the result of the trial?

O5: Exactly.

EA: Ok, ok that's very interesting for me to hear, that's very important for me to hear. And then [pages rustling], the headaches, the intermittent headaches that you get on and off

O5: No I don't, it's not like something that I get on and off. The headaches they come sometimes after hard working, like from peer pressure from work, and then I had that tension headache, and if I relax [EA: Oh okay] or I take the Panado and then it goes. It's not something that I will say that it's a problem or anything.

EA: How often do you think you get this?

O5: It depends with how much pressure do I get [EA: okay] [laughs]

EA: Do you remember any headaches just before or during the trial?

O5: No.



## South Africa (n=18)

Of 16 attending both visits, 15 (94%) reported differently

	General enquiry		Check list		Interview N=11
	D0*	D4-7	D0*	D4-7	D7-14
Medical history	NA	NA	+9		+4
Adverse events	18	5	+12	+8	+1 (night sweats)
Meds	16	1	+20	+3	+4

\*NB on trial, before 2<sup>nd</sup> dosing period

Additional AEs mild/unlikely

No additional meds prohibited

No change in eligibility

11 interviews/2 focus groups

## Tanzania (n=80)\*

At least 16 reported differently

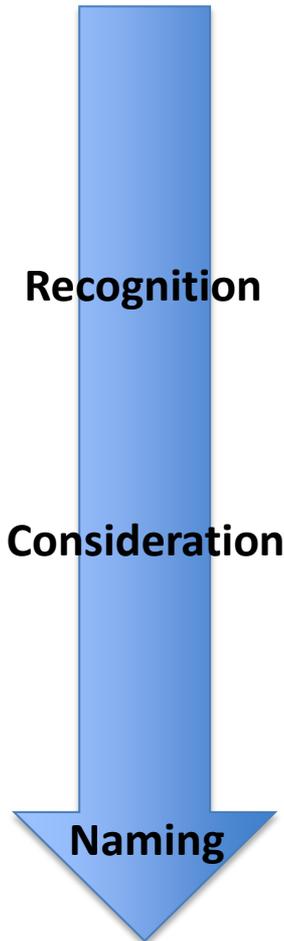
	General enquiry		Check list		Interview N=16
	D0	D7	D0	D7	D7
Medical history	58	NA	+53	NA	+8
Adverse events	NA	1	NA	0	+1 (palpitations)
Meds	18	12	+2	0	+10

\*Preliminary data (trial ongoing)

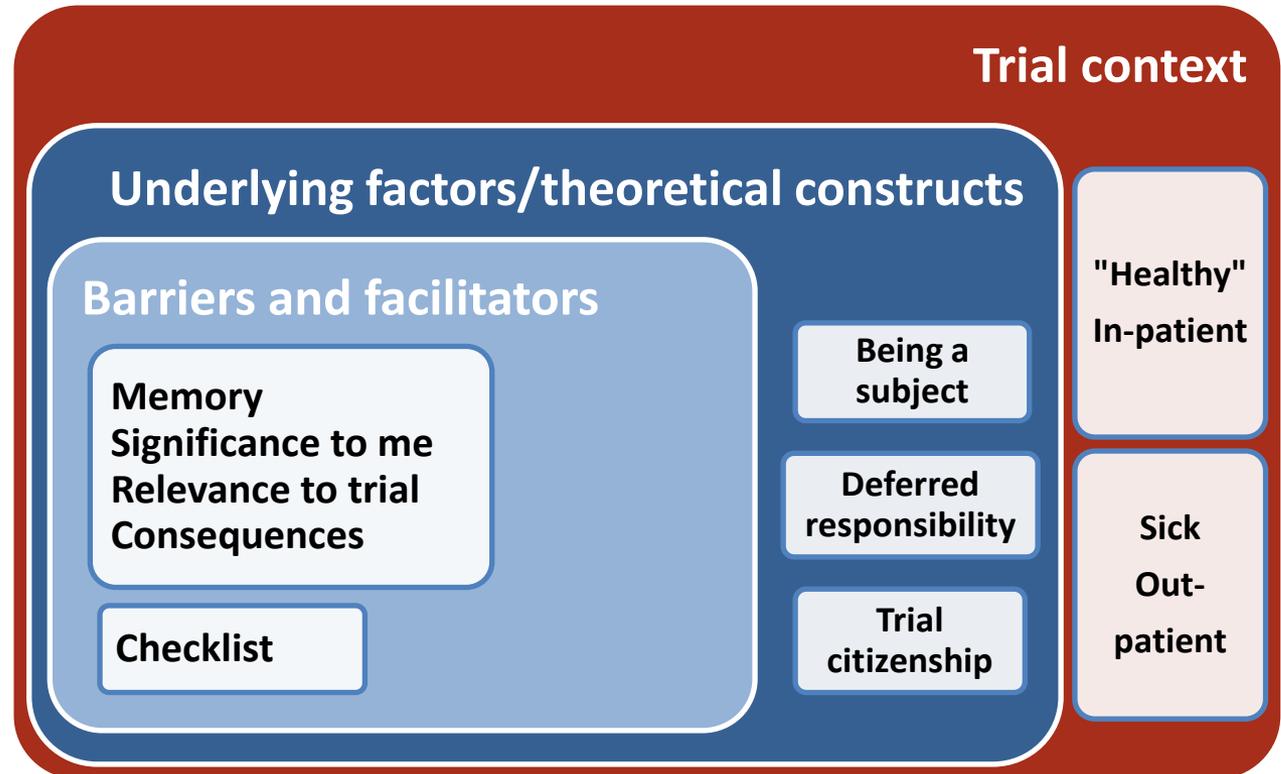
**1 possible prohibited antimalarial**

16 interviews/2 focus groups

**EXPERIENCE**



**REPORT**



# Barriers & facilitators

## Memory

Mild, intermittent, resolved health issues  
versus severe, persistent  
ARVs versus other medicines

## Significance to me

Bothersome, current, severe, persistent,  
versus intermittent, unimportant, secondary  
Comparisons to previous severe sickness  
Normalising and defining sickness  
Delayed reporting of some medicines



*“You may suffer every part of your body, so I don’t think that you can tell the doctor, one part after another. You may decide to tell him the basic problem”*

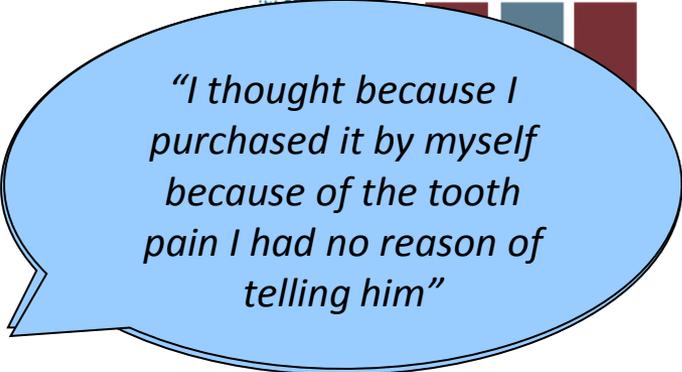
# Barriers & facilitators

## Relevance

Not necessary to report if not asked

Not relevant to the trial/consultation

Thought due to something else (activities rather than malaria)

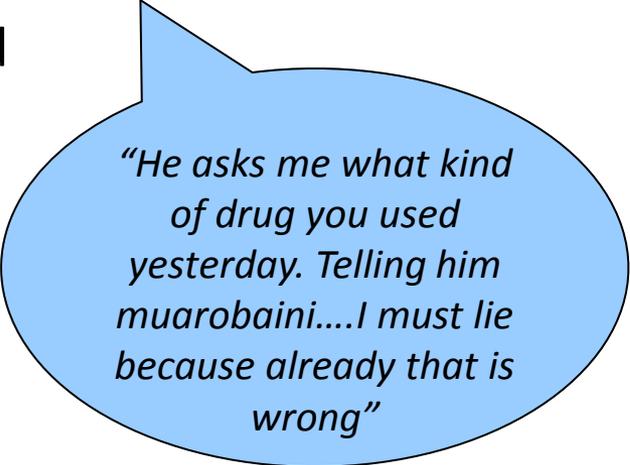


*"I thought because I purchased it by myself because of the tooth pain I had no reason of telling him"*

## Consequences

Fear of doing something wrong (trial or otherwise)

Fear of severe illness being diagnosed



*"He asks me what kind of drug you used yesterday. Telling him muarobaini....I must lie because already that is wrong"*

## Naming

Routine versus occasional

Prescribed versus 'street'

Spoken about versus hidden

# Underlying factors (theoretical constructs)



## Being a subject

Recruited, told what not to take

*"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?"*

## Deferred responsibility

Doctor has the knowledge to prompt me to reveal specific more information

Feeling bad but a participant was *"fair to the doctor"* for reporting and now *"she can't work with us"*

## Trial citizenship

Knowledge of and allegiance with the investigators' objectives

# Different trial contexts



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

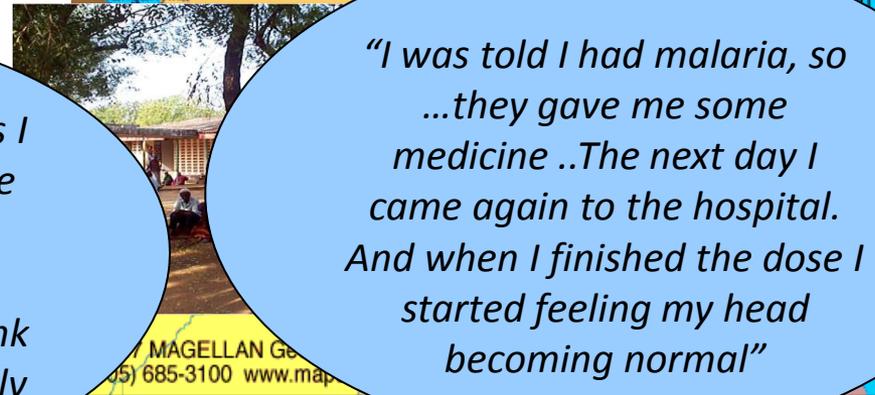


*"Somebody will say 'Guys I am feeling this, is anyone feeling it?' And then because that one said no..then you will also think 'Ah maybe it's me. It's only me'."*



Sick, outpatients accessing normal clinical care

*"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"*





## **Checklists overcame some barriers common to both trials despite different designs/contexts**

But not all.....

Need to think creatively about what constitutes an optimal questioning tool or approach

How do we overcome deferred responsibility?

Questions may be considered less relevant than tests/exams

Despite measurement errors potentially impacting on trial outcomes and meta-analyses, is there a limit to sensitivity?



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## Trial context

### Underlying factors/theoretical constructs

#### Barriers and facilitators

Memory  
Significance to me  
Relevance to trial  
Consequences

Checklist

Being a  
subject

Deferred  
responsibility

Trial  
citizenship

"Healthy"  
In-patient

Sick  
Out-  
patient