

Challenges in eliciting safety data from trial participants

Allen E¹, Barnes KI¹, Mushi AK², Massawe I², Staedke SG³, Mehta U⁴, Vestergaard LS⁶, Lemnge MM², Chandler CIR³

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



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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[®] 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

The screenshot shows the NVivo software interface. The main window displays a tree node structure for a project named 'ACTPR16_190911.nvp'. The tree is organized into folders: 'Free Nodes', 'Tree Nodes', 'Cases', 'Relationships', 'Matrices', 'Search Folders', and 'All Nodes'. The 'Tree Nodes' folder is expanded, showing a hierarchy of nodes. The selected node is '01 Facilitators and barriers to reporting', which contains several 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 further expanded, showing a list of text excerpts. The selected excerpt is: '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 [05: no I didn't], can you tell me the reason why maybe you didn't mention that? I am just interested in finding out.' The right-hand pane shows a list of text excerpts, with the selected one displayed in a larger font. The bottom status bar shows 'EA: 2017 Items, Nodes: 142, References: 174, Editable, Line: 404, Column: 9'. The Windows taskbar at the bottom shows the system tray with the time '10:58 AM' and the date '10/26/2017'.



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 2nd 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

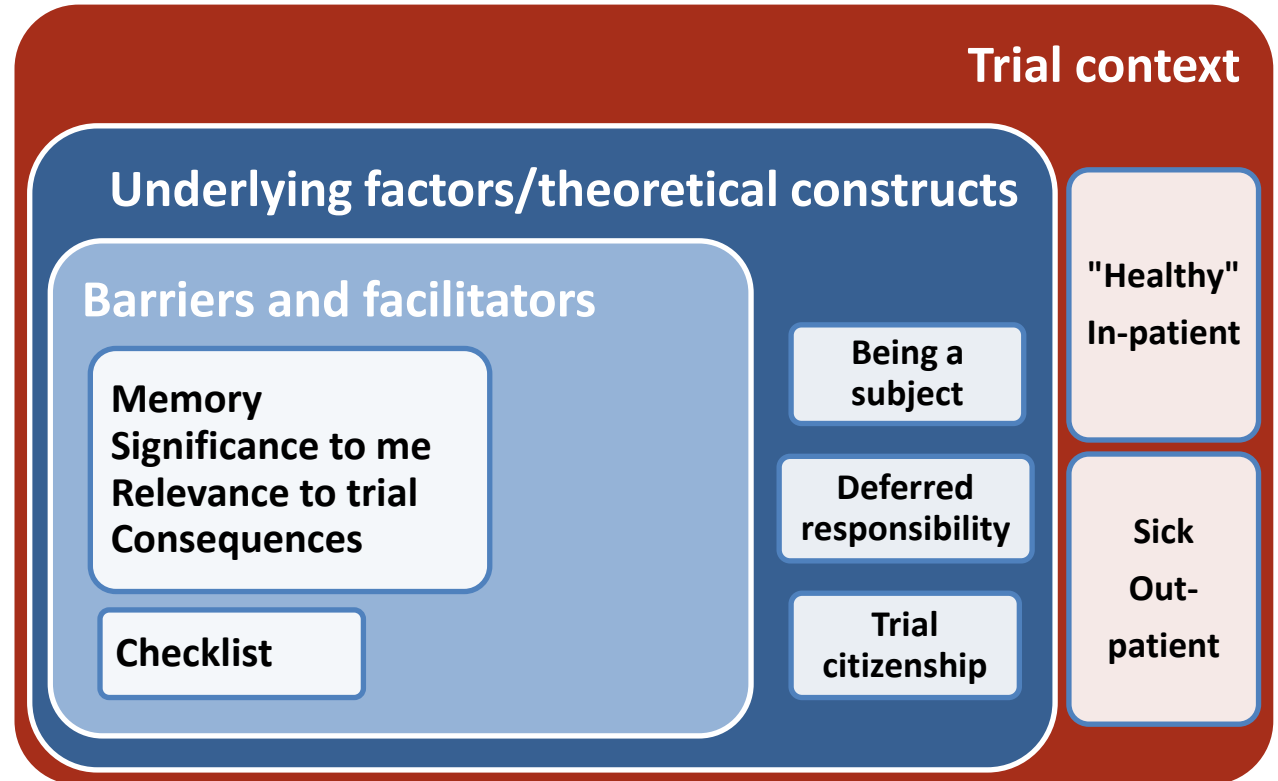
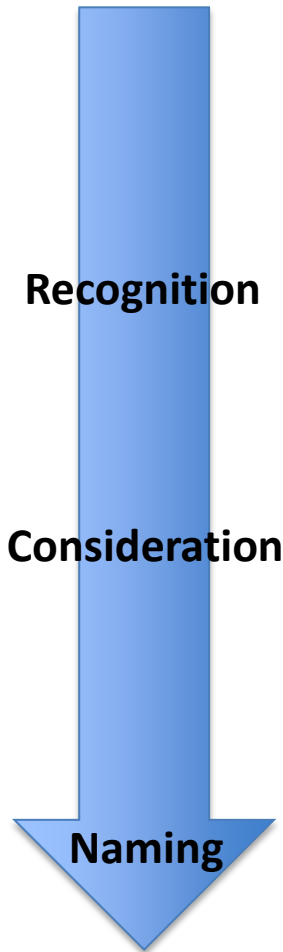
	General enquiry		Check list		Interview N=16
	D0	D7	D0	D7	D7
Medical history	58	NA	+53	NA	+8
Adverse events	NA	1	NA	0	+1 (palpitations)
Meds	18	12	+2	0	+10

*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”

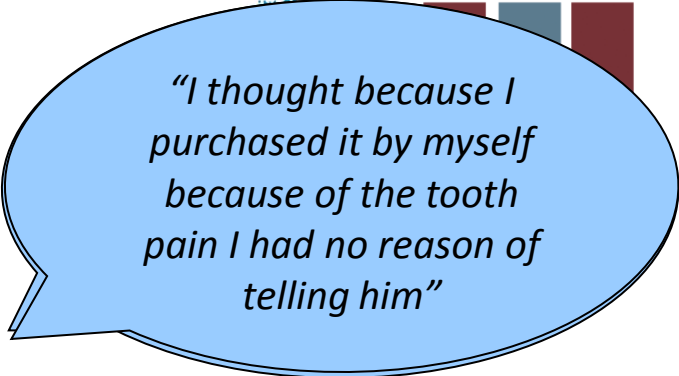
Barriers & facilitators

Relevance

Not necessary to report if not asked

Not relevant to the trial/consultation

Thought due to something else (activities rather than malaria)

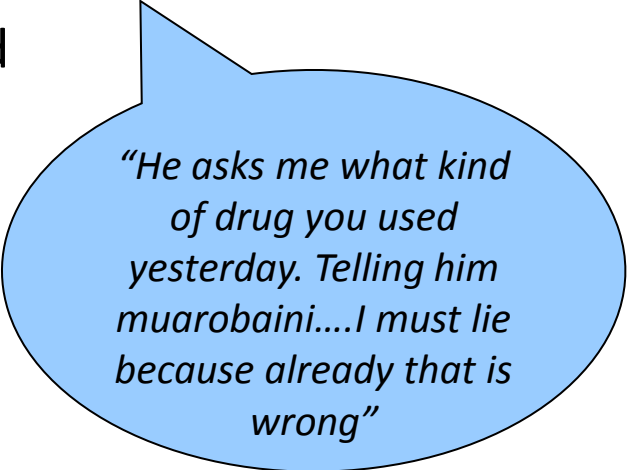


"I thought because I purchased it by myself because of the tooth pain I had no reason of telling him"

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



Sick, outpatients accessing normal clinical care

"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'."

"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