Challenges in eliciting safety data from trial participants

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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

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±)

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)

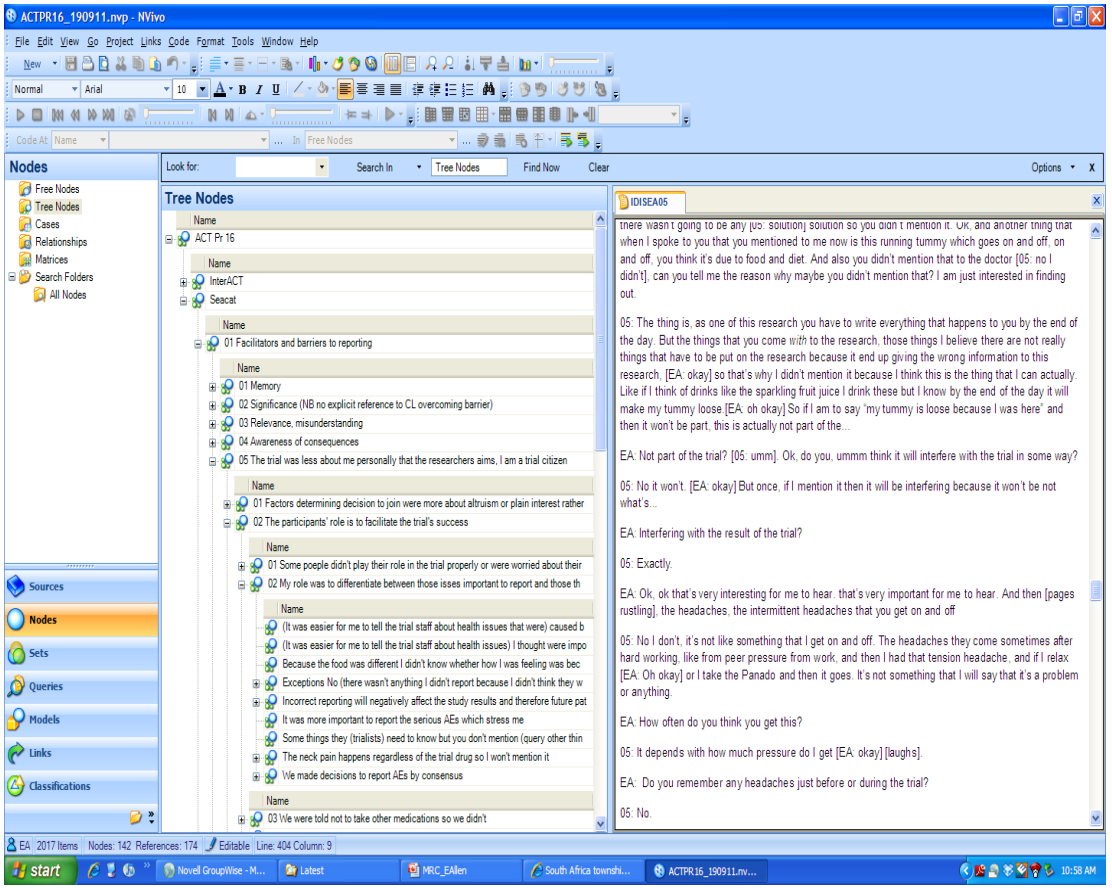
In-depth interviews & focus group discussions

Selection criteria

Those reporting differently between general enquiry/checklist

- Narrative

- Explanation



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

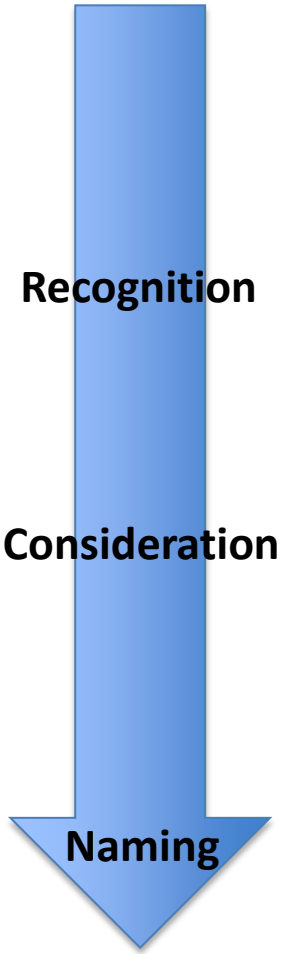
	General enquiry		Check list		Interview N=16
	D0	D7	D0	D7	D7
Medical history	58	NA	+53	NA	+8
Adverse events	NA	1	NA	0	+1 (palpitations)
Meds	18	12	+2	0	+10

*Preliminary data (trial ongoing)

1 possible prohibited antimalarial

16 interviews/2 focus groups

EXPERIENCE



REPORT

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

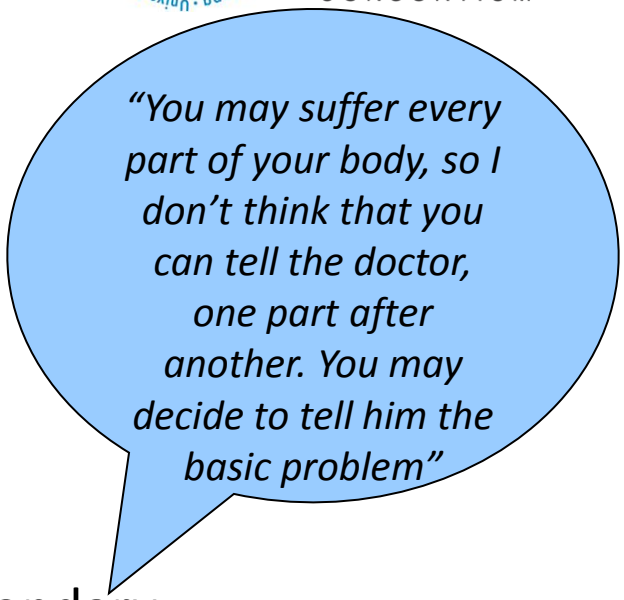
Barriers & facilitators

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

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

Naming

Routine versus occasional

Prescribed versus 'street'

Spoken about versus hidden

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

Underlying factors (theoretical constructs)

Being a subject

Recruited, told what not to take

Deferred responsibility

Doctor has the knowledge to

prompt me to reveal specific more information

"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?"

Trial citizenship

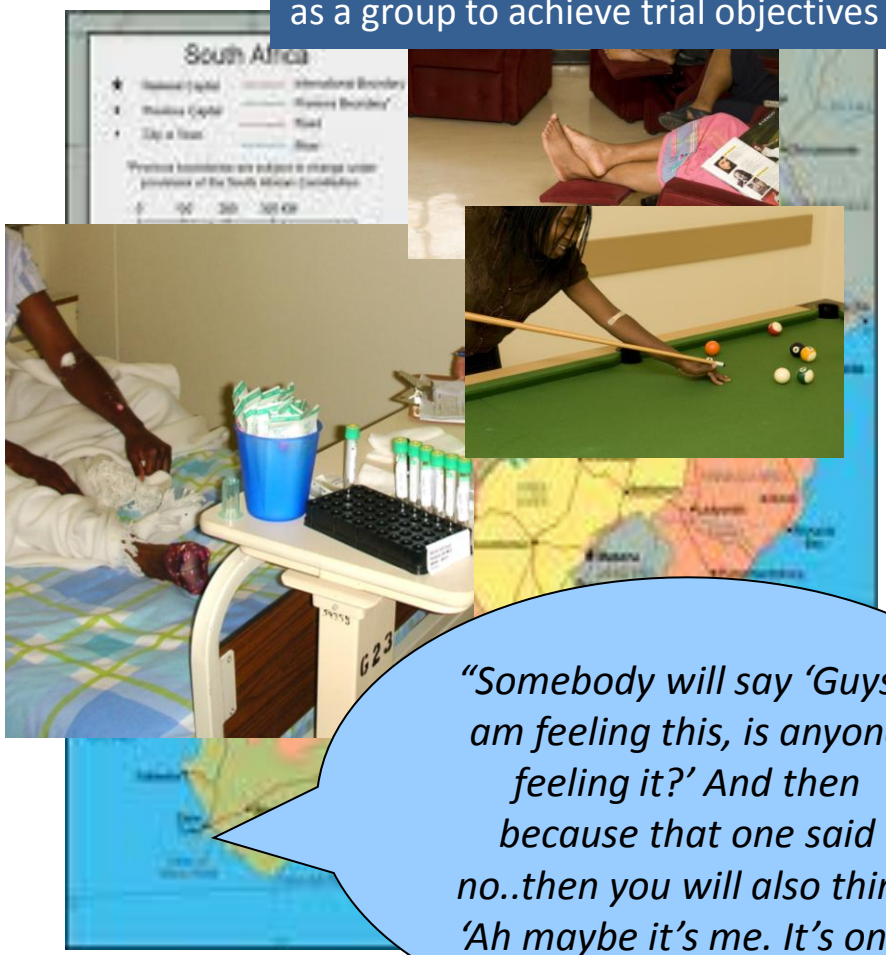
Knowledge of and allegiance with the

investigators' objectives

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

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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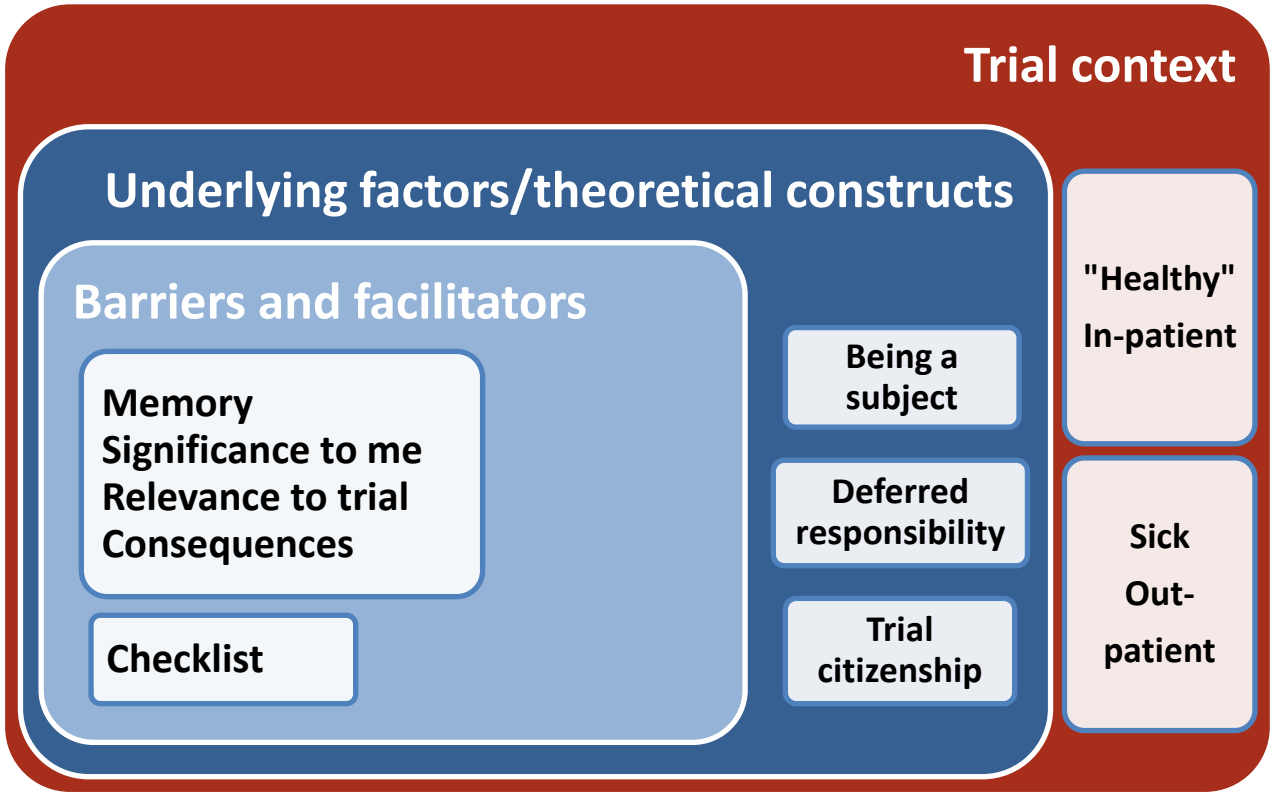
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