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

Elizabeth Allen, University of Cape Town, South Africa
Adverse events: the more you search, the more you find

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 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

General enquiry

Verbal checklists

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

2 occasions (pre-dose & 4-7 days post-dose)
Mixed-method study cont.

Results

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

<table>
<thead>
<tr>
<th></th>
<th>South Africa</th>
<th>Tanzania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical histories</td>
<td>4</td>
<td>285</td>
</tr>
<tr>
<td>Adverse events</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Meds</td>
<td>17</td>
<td>196</td>
</tr>
</tbody>
</table>

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

Sick, outpatients accessing normal clinical care

“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?”

“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”

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

www.actconsortium.org/safetydatacollection
Thank you for joining us!

Recording will be shared. Please ensure you are on our mailing list:

www.actconsortium.org/newsletter

For any questions or comments, contact

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