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The quality of informed consent: mapping the landscape. A review of empirical data from developing and developed countries

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Abstract

Objective—Some researchers claim that the quality of informed consent of clinical research participants in developing countries is worse than in developed countries. To evaluate this assumption, we reviewed the available data on the quality of consent in both settings.

Methods—We conducted a comprehensive PubMed search, examined bibliographies and literature reviews, and consulted with international experts on informed consent in order to identify studies published from 1966 to 2010 that used quantitative methods, surveyed participants or parents of paediatric participants in actual trials, assessed comprehension and/or voluntariness, and did not involve testing particular consent interventions. Forty-seven studies met these criteria. We compared data about participant comprehension and voluntariness. The paucity of data and variation in study methodology limit comparison and preclude statistical aggregation of the data.

Results and Discussion—This review shows that the assertion that informed consent is worse in developing countries than in developed countries is a simplification of a complex picture. Despite the limitations of comparison, the data suggest that: (1) comprehension of study information varies among participants in both developed and developing countries, and comprehension of randomisation and placebo controlled designs is poorer than comprehension of other aspects of trials in both settings; and (2) participants in developing countries appear to be less likely than those in developed countries to say they can refuse participation in or withdraw from a trial, and are more likely to worry about the consequences of refusal or withdrawal.

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Introduction

Many prospective research participants in developing countries have little formal education, lack familiarity with biomedical research and consent procedures, and have limited access to healthcare services. Consequently, it is widely believed that they have more difficulty comprehending study information and providing voluntary consent than do their counterparts in developed countries.[1–11] Such views are echoed in ethics guidelines such as those of the Council for International Organizations of Medical Sciences (CIOMS),[12] in a report by the National Bioethics Advisory Commission,[13] and in the popular press. For instance, a front-page New York Times article framed the problems with comprehension in a trial in the Ivory Coast as a matter of an impenetrable wall between scientific complexity and the ability of locals to understand it—one participant was described as "still not grasp [ing]—even after repeated questioning—what a placebo is or why she might have been given that instead of a real medicine".[14]

But what do we know about the quality of informed consent in developing country research? Does available evidence demonstrate that the quality of informed consent from developing country participants is worse than the quality of informed consent from participants in developed nations?

To begin addressing these questions, we reviewed and compared available data on the quality of informed consent from research in both developing and developed countries. We identify similarities and differences between studies of consent in developed and developing countries, highlight gaps in the available data, and make recommendations for future research on the quality of informed consent.

Methods: search strategy and selection criteria

We conducted a comprehensive PubMed search using the Medical Subject Headings (MeSH) terms *informed consent, comprehension* and *decision making* in combination with *clinical trials* or *randomized controlled trials* (box 1). In addition, we examined bibliographies,[15] literature reviews[16][17] and reference lists from relevant papers, and consulted with international experts on informed consent to clinical research.

We included studies that met four criteria: (1) used quantitative methods to study informed consent (to allow for comparison of relatively similar data sets); (2) surveyed participants or paediatric participants' parents in actual clinical trials rather than hypothetical scenarios (as we are concerned with what participants understand and how they make decisions in real trials); (3) did not test informed consent interventions aimed at improving its quality (to avoid confounding results); and (4) assessed at least one of two domains critical to measuring the quality of informed consent: comprehension of study information and voluntariness of consent. While some published data on disclosure exist, there are little to no comparable data from non-intervention utilising trials that evaluate understanding and comprehension relative to the quality of disclosure. A total of 427 studies were identified through the PubMed search (figure 1) and 79 from bibliographies, literature reviews, reference lists and consultations with experts. Of those 506 studies, 47 met all four criteria: 18 studies evaluated the quality of informed consent in trials in developing countries and 32

studies evaluated the quality of informed consent in trials in developed countries[i] (tables 1 and 2). Identified studies were reviewed by the authors and information extracted regarding the type and location of the clinical trial, the sample size, and the method and timing of assessing informed consent. Data about participants' comprehension of trial information and voluntariness were extracted, including understanding of the purpose and nature of the research, the risks and side effects, and randomisation and placebo controlled design (tables 3–5), as well as perceived pressure and participant knowledge of the right to refuse to enrol or withdraw from a trial (table 6). Direct comparison or meta-analysis of study data was not feasible, as the relevant studies did not employ a uniform methodology or study design.

Results

Study characteristics

Eighteen studies conducted in 11 different developing countries examined the consent of participants in clinical research on vaccines, nutritional supplements, HIV treatments, immune correlates in children, diarrhoeal disease in children, anti-malarial drugs and genetics (table 1). Sample sizes ranged from 33 to 700 research participants. Seven studies interviewed a parent of a participating child,[18212224262933] and of those seven, three interviewed only the mothers.[222433] Thirteen studies[19–212326–3335] used structured or semi-structured interviews, while five used questionnaires.[1822242534] In nine studies, participants were interviewed close to the time of consent[18232426282933–35] and in eight others interviews were conducted 1–14 months or longer after the participant gave consent.[19–2225273031] In one study, the timing was not specified.[32]

Thirty-one studies, conducted in eight developed countries, examined the consent of participants involved in oncology, cardiology, gynaecology, HIV, analgesics/anaesthesia, neurological, antidepressant, antipsychotic, emergency management, arthritis, paediatric asthma, paediatric febrile convulsion, diabetes, malaria and genetics research (table 2). Sample sizes ranged from 21 to 570 research participants. Six studies surveyed the parents of children in paediatric trials.[404245485457] Sixteen studies used structured interviews,[193839424547485054575860–64] nine used mailed surveys,[374143464951–5359] and six used questionnaires.[183640445556] In eight studies, questions were asked close in time to when consent was given, in each case within 48 h of consent[1839404248556064]; the remaining 23 studies surveyed participants weeks to months after consent.[1936–384143–4749–5456–5961–63]

Comprehension and recall of trial information

Participant understanding of research purpose, risks/side effects and design varied substantially across informed consent studies from both developing and developed countries. Across studies, comprehension of trial purpose or nature appeared to be better than comprehension of trial design and randomisation.

Trial purpose and nature—Available data show no substantial difference between participants in developing countries and those in developed countries with respect to their

[i]Ellis[18] and Marshall[19] each studied informed consent in both a developed and a developing country.

understanding of trial purpose, defined as the goal of a given clinical trial (table 3). In the developed country studies that measured it, understanding of trial purpose ranged from 10% of US males who understood the purpose of a variety of trials they were participating in[62] to 100% of Canadian participants who understood the purpose of a neurooncology trial.[45] Understanding of trial purpose in developing country studies also varied, ranging from 26% of Malian parents who understood the purpose of a malaria trial for their children[26] to 90% of mothers with children in a paediatric influenza trial in The Gambia.[33] Similarly, reported understanding of trial nature, assessed by participants' understanding that they were participating in research and of the investigational and experimental nature of research interventions, varied from 31% of participants in a US phase 1 oncology trial[50] to almost 100% of participants in both a Swedish and a Finnish trial,[5159] and from 47% of women in a Bangladeshi nutritional trial for iron supplements[32] to 100% of women in an HIV trial in Côte d'Ivoire.[30]

Risks/side effects—The percentage of participants who could recognise or name trial side effects and risks also ranged widely among the studies reviewed (table 4). Reported understanding of side effects varied depending on how the questions were framed—more participants were able to recognise side effects from a list than were able to name or explain them in response to open-ended questions. For example, 86% of participants in a US analgesic trial recognised at least one side effect from a list, but only 48% were able to name at least one without the help of a list.[58] In a US rheumatoid arthritis trial, 30% responded that they knew the trial drugs were not completely safe, but were not asked to recognise or name the specific risks of the drugs.[44]

In consent studies of developing country trials, 79% of participants in a South African vaccine trial knew the risks involved[22] and 97% of Thai participants recognised possible side effects of an experimental HIV vaccine,[35] yet only 7% of Malian parents recognised that the investigational vaccine being given to their child might have side effects.[26]

Randomisation and placebo trial design—Understanding of randomisation also varied among participants in both developing and developed country trials, but across all studies, understanding of randomisation was low compared to understanding of other aspects of a trial (table 5). In developed country studies, understanding of randomisation appeared to vary according to how close to actual consent it was measured. For example, 68% of parents understood randomisation when asked within 48 h of consent in US paediatric oncology trials,[48] and as many as 79% understood randomisation in an HIV vaccine trial when assessed immediately after disclosure.[55] Yet fewer than half of the participants were reported to comprehend randomisation in six developed country studies in which understanding was assessed months or years after consent.[444647515363]

Five developing country studies measured understanding of randomisation (table 5); four of those five measured it within 1 week of consent.[1820262829] Comprehension of randomisation ranged from as high as 90% of parents whose children were enrolled in a malaria vaccine trial in Mali[18] to as low as 19% of parents whose children were enrolled in a malaria treatment trial in Uganda.[29]

Between 64% and 88% of participants understood the study design in six developed country trials,[41,44,46,53,64] yet only 39% of the participants in a set of Canadian trials recalled their own chance of receiving placebo, and 29% of them "thought that the doctor [had known] what kind of medication they were taking".[46] Knowledge of placebo was measured in three developing country studies: 10% of mothers enrolling children in a Gambian trial understood the placebo control design,[33] 13% of Ghanaian trial participants knew that not all trial capsules were the same,[23] and 49% of South African participants knew they had a 50% chance of receiving placebo.[27]

Although measured infrequently, individuals' understanding of research design diverges from their understanding of how it specifically applies to them. In one Thai HIV treatment trial, 31% correctly responded that half the participants would get the investigational drug, yet 48% said they had a 50/50 chance of receiving it.[28] In a Ugandan malaria trial, 19% of parents knew that not all children would receive the same treatment, even though 84% recalled being told about treatment assignment.[29] Similarly, in a US rheumatoid arthritis trial, 87% of participants said that some people in the trial would get placebo, but only 50% thought they personally could receive placebo.[44]

Voluntariness

Data on voluntariness is organised into two categories: (1) participants' perceptions of pressure (not reported in a table); and (2) participants' knowledge of the right to refuse or withdraw from participation (table 6).

Pressure—Questions assessing perceptions of pressure differed across informed consent studies—some focused on whether or not participants knew or felt that participation was voluntary, while others asked more specific questions about the source and amount of pressure felt by participants.

Most (90%–99%) participants in a US hypertension trial, a Canadian neuro-oncology trial and UK paediatric trials reported no pressure to participate[19,38,40] or reported that participation was voluntary.[52] At the same time, 31% of US oncology and cardiology trial participants said that they felt that they had little other choice than to participate,[54] 25% of parents in a Netherlands paediatric oncology trial indicated that they felt obliged to participate[53] and 18% of Danish participants in an acute myocardial infarction trial reported feeling 'under pressure', although 70% said the decision was 'fully theirs'.[41]

Five developing country informed consent studies measured general perceptions of pressure and voluntariness. Most mothers (95%) in a Ghanaian paediatric trial[21] and most participants (99%) in a South African influenza vaccine trial[27] said participation was voluntary. Similarly, most parents in an Indian paediatric trial (98%) reported that they joined the study freely without any pressure or compulsion.[24] In contrast, in another South African trial, 84% of the evaluation group and 93% of the sensitisation group reported feeling that participation was compulsory.[34]

In consent studies that distinguished sources of pressure, more trial participants reported feeling pressure from their disease or circumstances than from other people. Although 29%

of US phase I and phase II oncology trial participants said that their physician did not actively want them to make their own decision,[61] only 14% in a Swedish gynaecology trial,[59] 7% in another US oncology trial[62] and 6% in a set of varied US trials reported feeling pressure from a clinician.[39] In the same oncology study in which 7% reported pressure from a clinician and 9% from their families, a full 75% reported pressure due to their progressive cancer.[39] In another US paediatric oncology trial, 70% of the parents cited high levels of distress and 'feeling overwhelmed' during the consent process.[45] Few participants in developed country trials reported pressure from anticipated consequences of withdrawing: 98% of UK anaesthesia trials participants,[52] 86% of Canadian neuro-oncology trial participants[38] and 85% of Danish cardiology trial participants[41] knew that refusal to participate would *not* compromise their care.

In developing country studies, reported pressure from others was also generally low, ranging from 6% of participants reporting pressure from spouses, family or the research team in a Ugandan paediatric malaria treatment trial[29] to 26% reporting pressure from village elders in a Malian paediatric vaccine trial.[26] Reported pressure came from various sources, for example, from village elders (26%), the research team (12%) and a spouse (7%) in the aforementioned Malian study,[26] and from a close friend (15%), a family member (7%) or their doctor (2%) in an HIV treatment trial in Thailand.[28] Similarly, in a Ugandan paediatric trial, 15% of parents reported feeling pressure from others, including spouses (6%), family or friends (6%) or the research team (6%), but 58% reported pressure because of their child's illness.[29] However, in one Gambian trial, 9% of mothers offered spontaneously and 36% agreed when directly questioned that it would have been hard to refuse participation–some reported feeling group pressure after watching other mothers agree to participate.[33]

Participants in developing countries reported pressure from fear of the consequences of withdrawing. Although in one South African trial, 88% said their usual care would not be affected if they refused,[27] 87% of participants in a Bangladeshi trial felt that the trial offered such advantages that they couldn't refuse.[32] Similarly, 32% of the evaluation study group and 23% of the sensitisation group in a South African perinatal HIV transmission trial thought that care would be compromised if they did not participate,[34] and 44% of parents in a paediatric malaria vaccine trial in Mali said they would lose healthcare access if they withdrew.[26]

Knew they could refuse or withdraw—The clearest differences between respondents in developed and developing country informed consent studies were related to knowledge of the right to refuse to participate in research or to withdraw (table 6). In 15 of 18 developed country studies that measured this, more than 75% of trial participants knew they could withdraw or refuse,[181936374043444952–5460–6264] and in 10 of these studies, 90% or more said they could withdraw from research.[18193637404344495360] In one US paediatric oncology trial, 90% of the majority race English speaking parents, 78% of the minority race English speaking parents and 60% of the minority race non-English speaking parents knew they had a right to withdraw their children from the trial.[48]

In contrast, in five of 15 developing country studies that measured it, less than half of respondents knew they could withdraw from research.[222630–32] As few as 10% of mothers in

Mali knew they could withdraw their child from a malaria vaccine trial at any time,[26] and 27% of participants in an HIV trial in Côte d'Ivoire knew they could withdraw at any time.[30] However, in some developing country trials a higher percentage of participants knew they could withdraw or refuse, for example 50% of parents in a paediatric diarrhoeal trial[21] knew they could leave the trial at any time, >90% of adults and parents of children in a Malian malaria vaccine trial[18] knew they could withdraw from the trial and 88% of Thai vaccine participants knew they could 'refuse to participate at any time'.[35] One study of a South African HIV trial[17] reported that 93% of the women knew they had the right to quit, but 98% said they believed the hospital would not allow them to quit.[34]

Discussion

This is the first comparison of quantitative studies of the quality of informed consent from individuals participating in clinical trials in both developed and developing countries. Our review shows that the assertion that research informed consent is worse in developing countries than in developed countries is an oversimplification of a complex picture of the quality of consent. The quality of informed consent depends on the type and amount of information disclosed, adequate comprehension of trial information, and a voluntary decision to enrol. The existing data, which use comprehension and voluntary decision-making as measures of the quality of consent, do not support a categorical difference between the quality of consent from individuals in developed countries and the quality of consent from individuals in developing countries.

A paucity of data, especially from participants from developing countries, as well as variations in trial type, study methodology, sample size, measures used and timing of data collection relative to obtaining consent, limits comparison and statistical aggregation. Nonetheless, these data suggest certain important trends and point to the need for further research.

Our review highlights the following: (1) comprehension of study information varies among trial participants in both developed and developing countries, and comprehension of randomisation and placebo controlled designs is generally lower than comprehension of other aspects of a trial; (2) research participants report different sources of pressure to enrol, and those in developing countries are less likely than those in developed countries to say they can refuse or withdraw from participation, and more likely to worry about the consequences of refusal or withdrawal.

Data show a range of understanding of trial information in both developed and developing country trials. Individuals across studies tended to know that they were involved in research and often responded correctly to questions about the nature and purpose of the research, yet participants everywhere had more difficulty understanding information about trial design, randomisation and placebo controls. Not only are these methods and concepts unfamiliar to many people, but such methods may be contrary to their expectations or hope for therapeutic benefit, making them more difficult to comprehend. Notably, some studies reveal discrepancies between participants' understanding of what will happen in a trial and how this information will affect them *directly*. Knowledge of facts and appreciation of those facts are

different aspects of understanding, both of which are important to *informed* consent.[65] This discrepancy is a challenge for informed consent everywhere, and although few studies attempted to measure it, the present data do not suggest a difference in appreciation between developed and developing country participants.

Second, the data on refusal and withdrawal indicate a troubling trend. Finding it difficult to refuse participation in or withdraw from a trial, feeling pressure to join or stay enrolled in a trial, or worrying about the consequences of withdrawing all relate to the voluntariness of an enrolment decision. Studies which used these measures of voluntariness show that a disquieting number of participants, and more in developing country trials than developed country trials, do not know or do not believe that they can refuse to participate or can withdraw from research. Few studies probed these responses further to explain why participants felt they could not refuse or withdraw. Possible explanations include deference to authority, cultural norms, or a founded or unfounded fear of not being able to access needed care.

Lastly, while investigations of the impact of pressure on voluntariness were limited, overall few research participants report feeling pressured to participate in research, and those that did often felt pressure from their circumstances–such as worsening illness or fear that care would be withdrawn—more than from other people. Participants in developing countries were more likely to report pressure from fear of the consequences of withdrawing, including decreased access to healthcare. These issues merit further study.

Recommendations for future research

These data reveal that there is much to be done to improve the quality of informed consent in both developed and developing countries and that additional research would facilitate definitive conclusions about the quality of informed consent around the world. Currently available evidence regarding the effectiveness of strategies to improve consent is limited.[66–68] Variation in methodology, trial types and populations across studies reviewed raised challenges about how to accurately understand and measure the quality of informed consent. Design and implementation of improvement measures depends on careful attention to, and rigorous delineation of, what the quality of consent entails.

Studies of the quality of informed consent would be greatly enhanced by a core set of validated questions that measure the comprehension and voluntariness of participants at the time of decision-making, and by comparison of participants from similar medically defined groups participating in similar types of research. Studying the quality of consent in multi-national trials, such as was done in one multi-site hypertension study we reviewed,[19] would allow for useful comparisons between developed and developing countries. Additionally, more detailed and comprehensive studies of voluntariness are needed, including investigation of sources of pressure to participate and fears about withdrawal or refusal. Future studies should include detailed investigation of associations between cultural norms and attitudes, and socio-demographic characteristics such as education, literacy and socioeconomic status to better understand the impact of these factors on informed consent in both developed and developing countries. Innovative strategies and rigorous studies are

sorely needed to facilitate improvement in informed consent to better satisfy one of the fundamental requirements of ethical research.

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Box 1

MeSH terms strategy

(informed consent[mh] AND (Comprehension[mh] OR decision-making[mh])

AND (randomized controlled trials as topic[mh] OR clinical trial as topic[mh])

AND (Humans[Mesh] AND English[lang]))

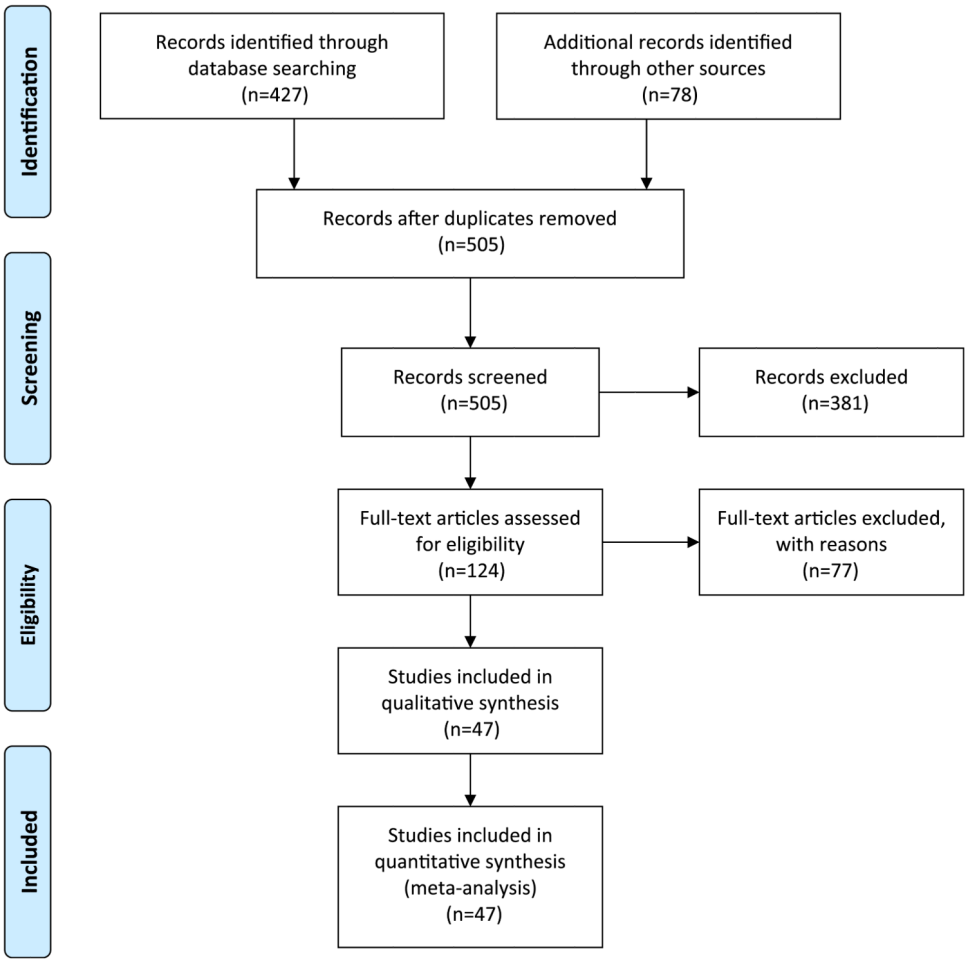

Figure 1.

PRISMA 2009 flow diagram (adapted from Moher D, Liberati A, Tetziaff J, *et al*; The PRISMA Group. Preferred reporting items for systemic reviews and meta analyses: the PRISMA statement. *PLoS Med* 2009;**6**: e1000097. For more information, visit http://www.prisma-statement.org). This figure is produced in colour in the online journal—please visit the website to view the colour figure.

Table 1

Developing country consent studies

Authors	Country	Sample	Type of clinical research	Method of evaluation
Ellis *et al*, 2010[18]	Mali	89 M and F	Malaria vaccine phase 1 trial	Questionnaire administered after IC document reviewed but before consent
Vallely *et al*, 2010[20]	Tanzania	99 F	Placebo controlled trial of HIV vaginal microbicide	Interviews at 4, 24 and 52 weeks
Sarkar *et al*, 2009[21]	India	368 Parents	Birth cohort study of diarrhoeal disease	Structured interviews 3–7 months post-trial
Oduro *et al*, 2008[22]	Ghana	270 Mothers	Paediatric trials evaluating immune correlates of protection against malaria	Questionnaire administered at end of study
Hill *et al*, 2008[23]	Ghana	60 F	Vitamin A supplementation trial	Semi-structured interviews after consent
Minnies *et al*, 2008[24]	South Africa	192 Mothers	Paediatric case–control trial of immune correlates against severe childhood TB	Self-administered questionnaire with staff help if necessary, within 1 h of consent
Kaewpoonsri *et al*, 2006[25]	Thailand	84 M and F	Malaria drug trials	Interview at third follow-up visit
Marshall *et al*, 2006[19]	Nigeria	307 M and F	Genetic studies of hypertension	Interviews administered at variable times usually long after consent
Krosin *et al*, 2006[26]	Mali	163 Parents	Paediatric malaria vaccine prevention trial	Questionnaire within 48 h after consent
Moodley *et al*, 2005[27]	South Africa	334 M and F	Influenza vaccine trial	Interviews 4–12 months post-trial
Pace *et al*, 2005[28]	Thailand	141 M and F	HIV study of IL-2 effectiveness	Interviewers administered survey immediately after consent
Pace *et al*, 2005[29]	Uganda	347 Parents	Paediatric malaria treatment study	Interviews immediately after consent
Ekouevi *et al*, 2004[30]	Côte d'Ivoire	55 F	HIV mother-to-child transmission prevention trial	Interviews a median of 136 days after consent
Joubert *et al*, 2003[31]	South Africa	92 F	Trial of vitamin A for prevention of mother-to-child HIV transmission	Interviews a median of 14 months after consent
Lynöe *et al*, 2001[32]	Bangladesh	105 F	Nutritional trial of iron supplements for pregnant women	Interviews after consent
Leach *et al*, 1999[33]	The Gambia	137 Mothers	Paediatric trial of *Haemophilus influenzae* type B conjugate vaccine	Interviews within a week of consent
Karim *et al*, 1998[34]	South Africa	Evaluation study group: 56 F Sensitisation control group: 56 F*	Perinatal HIV transmission trial	Questionnaires administered before and after counselling and consent
Pitisuttithum *et al*, 1997[35]	Thailand	33 M and F	HIV vaccine trial with drug users	Questionnaire before signing consent

*To evaluate the informed consent obtained for the HIV testing that preceded induction into the perinatal transmission trial, researchers administered both pre- and post-counselling questionnaires to an evaluation study group (n=56). A sensitisation control group (n=56) received only post-counselling questionnaires, so as to measure the sensitising effect of the pre-counselling questionnaire given to the evaluation study group.

F, female; IC, informed consent; M, male.

Table 2

Developed country consent studies

Authors	Country	Sample	Type of clinical research	Method of evaluation
Ellis *et al*, 2010[18]	USA	171 M and F	Malaria vaccine phase I trial	Questionnaire administered after IC document reviewed but before consent
Ravina *et al*, 2010[36]	USA	149 M and F	Phase II Parkinson's trial	Self-administered questionnaire at final clinical trial visit
Bergenmar *et al*, 2008[37]	Sweden	282 M and F	Phase II and phase III oncology trials	Mail surveys sent within 3 days–2 weeks of consent
Knifed *et al*, 2008[38]	Canada	21 M and F	Neuro-oncology trial	Interviews within 1 month of IC
Agrawal *et al*, 2006[39]	USA	163 M and F	Phase I oncology trials	Interview immediately after consent
Franck *et al*, 2007[40]	UK	109 Parents	25 Different paediatric studies	Questionnaire taken immediately after and 3 months after consent
Marshall *et al*, 2006[19]	USA	348 M and F	Genetic studies of hypertension	Interviews long and variably after consent
Gammelgaard *et al*, 2004[41]	Denmark	103 M and F	Acute myocardial infarction trials	Mail survey sent to participants in the study 3 weeks after IC
Kodish *et al*, 2004[42]	USA	137 Parents	Paediatric leukaemia trial	Parent pairs interviewed within 48 h of consent
Lynöe *et al*, 2004[43]	Sweden	44 M and F	Chronic haemodialysis trials	Mail survey about 1 week after disclosure of information
Criscione *et al*, 2003[44]	USA	30 M and F	Rheumatoid arthritis trial	Questionnaire 1–4 weeks after consent
Kupst *et al*, 2003[45]	USA	20 Parents	Paediatric oncology trials	Interviews 1 month after IC
Pope *et al*, 2003[46]	Canada	190 M and F	Cardiology, ophthalmology and rheumatology trials	Mail survey 2–5 months after consent
Schats *et al*, 2003[47]	The Netherlands	37 M and F	Subarachnoid haemorrhage emergency management trials	Interviews 7–31 months after IC (median of 20 months)
Simon *et al*, 2003[48]	USA	Majority English speakers: 60 parents Minority English Speakers: 27 parents Minority non-English speakers: 21 parents	Paediatric oncology trials	Parents interviewed 48 h after consent
Joffe *et al*, 2001[49]	USA	207 M and F	Oncology trials, phase I, II and III	Mail survey 1–2 weeks after consent
Daugherty *et al*, 2000[50]	USA	144 M and F	Phase I oncology trials	Interviews within 1 week of first administration of investigational treatment
Hietanen *et al*, 2000[51]	Finland	261 F	Oncology trial of tamoxifen	Mail survey 5–17 months after consent
Montgomery *et al*, 1998[52]	UK	158 M and F	3 In-house and 3 multi-centre anaesthesia trials	Mail survey up to 24 months after consent
Van Stuijvenberg *et al*, 1998[53]	The Netherlands	181 Parents	Paediatric trial of ibuprofen for febrile convulsions	Mail survey up to 2–3 years after consent
ACHRE, 1996[54]	USA	570 M and F	Oncology and cardiology trials	Brief interviews followed by in-depth interviews
Harrison *et al*, 1995[55]	USA	71 M and F	HIV vaccine trial	Self-administered questionnaire after disclosure and before consent

Authors	Country	Sample	Type of clinical research	Method of evaluation
Harth *et al*, 1995[56]	Australia	62 Parents	Paediatric trial of oral asthma drug	Self-administered questionnaire 6–9 months after entered trial
Estey *et al*, 1994[57]	Canada	29 M and F	Not specified	Interviews 1–6 weeks after consent
Miller *et al*, 1994[58]	USA	168 M and F	Trial of analgesic drugs	Interviews 30–90 days after entered trial
Lynöe *et al*, 1991[59]	Sweden	43 F	Gynaecology trial of antiphlogistic drugs for fallopian tube inflammation	Mail survey 18 months after study
Benson *et al*, 1985[60]	USA	Depression study: 24 M and F Schizophrenia study: 24 M	Antidepressant trial and antipsychotic trial	Interviews immediately following IC
Penman *et al*, 1984[61]	USA	144 M and F	Oncology trials, phase II and III	Interviews 1–3 weeks after consent
Riecken *et al*, 1982[62]	USA	112 M *	50 Different trials	Interviews within 10 weeks of consent
Howard *et al*, 1981[63]	USA	64 M and F	Cardiology trial of β-blockers (BHAT) for acute myocardial infarction	Interviews 2 weeks–15 months after consent
Bergler *et al*, 1980[64]	USA	39 M	Hypertension trial of hydrochlorothiazide versus propranolol	Interviews and quizzes just after consent; repeated 3 months later

* The trial involved 156 participants, but only 112 indicated that they were aware that they were participating in a trial, and therefore only 112 were asked questions about voluntariness. ACHRE, Advisory Committee on Human Radiation Experiments; F, female; IC, informed consent; M, male.

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Table 3

Understanding of research nature and purpose*

Developed country studies			Developing country studies		
Author	**Country**	**Understood purpose**	**Author**	**Country**	**Understood purpose**
Knifed *et al*, 2008[38]	Canada	100%	Leach *et al*, 1999[33]	The Gambia	90%
Ravina *et al*, 2010[36]	USA	92.6%	Pace *et al*, 2005[28]	Thailand	88%
Franck *et al*, 2007[40]	UK	85%	Minnies *et al*, 2008[24]	South Africa	80.6%
Howard *et al*, 1981[63]	USA	80%	Pace *et al*, 2005[29]	Uganda	80%
Miller *et al*, 1994[58]	USA	73%	Kaewpoonsri *et al*, 2006[25]	Thailand	50%
Van Stuijvenberg *et al*, 1998[53]	The Netherlands	53%	Sarkar *et al*, 2009[21]	India	43%
Marshall *et al*, 2006[19]	USA	41%	Marshall *et al*, 2006[19]	Nigeria	39%
Benson *et al*, 1985[60]	USA	37% each in depression and schizophrenia studies	Krosin *et al*, 2006[26]	Mali	26%
Daugherty *et al*, 2000[50]	USA	31%	Joubert *et al*, 2003[31]	South Africa	28%, but 40% knew the substance being tested was vitamin A
Harth *et al*, 1995[56]	Australia	13%			
Riecken *et al*, 1982[62]	USA	10%			

Developed country studies			Developing country studies		
Author	**Country**	**Understood nature**	**Author**	**Country**	**Understood nature**
Knifed *et al*, 2008[38]	Canada	100%	Ekouevi *et al*, 2004[30]	Côte d'Ivoire	95%e100%
Criscione *et al*, 2003[44]	USA	100%	Moodley *et al*, 2005[27]	South Africa	95%
Hietanen *et al*, 2000[51]	Finland	100%	Minnies *et al*, 2008[24]	South Africa	85.4% knew was research; 36.7% knew there were no immediate benefits
Lynöe *et al*, 1991[59]	Sweden	98%	Vallely *et al*, 2010[20]	Tanzania	77% knew gel may not prevent HIV
Howard *et al*, 1981[63]	USA	92%	Hill *et al*, 2008[23]	Ghana	75% knew was research, but 93% thought trial capsules were a ‘medicine or vitamin’
Ravina *et al*, 2010[36]	USA	89% understood drugs were experimental †	Lynöe *et al*, 2001[32]	Bangladesh	47%
Ellis 2010[18]	USA	85%	Krosin *et al*, 2006[26]		26%
Penman *et al*, 1984[61]	USA	78%			
Gammelgaard *et al*, 2004[41]	Denmark	72%			

Developed country studies			Developing country studies		
Author	**Country**	**Understood purpose**	**Author**	**Country**	**Understood purpose**
Riecken *et al*, 1982[62]	USA	72%			
Bergenmar *et al*, 2008[37]	Sweden	~70%			
Kupst *et al*, 2003[45]	USA	55%			
Schats *et al*, 2003[47]	The Netherlands	38%			
Joffe *et al*, 2001[49]	USA	30%			

*Arranged from highest to lowest %.

†Yet only 57% knew that participation in the study was not part of usual Parkinson's disease treatment.

ACHRE, Advisory Committee on Human Radiation Experiments.

Table 4

Understanding of risks and side effects*

Developed country studies			Developing country studies		
Author	**Country**	**Understood risks or side effects**	**Author**	**Country**	**Understood risks or side effects**
Daugherty *et al*, 2000[50]	USA	100% named >1 side effect	Pace *et al*, 2005[28]	Thailand	98% recognised side effects
Harrison *et al*, 1995[55]	USA	89% recognised side effects	Pitisuttithum *et al*, 1997[35]	Thailand	97% recognised side effects
Knifed *et al*, 2008[38]	Canada	71% knew at least one general risk†	Minnies *et al*, 2008[24]	South Africa	79.2% knew risks
Benson *et al*, 1985[60]	USA	Depression study: 62% knew risks Schizophrenia study: 42% knew risks	Leach *et al*, 1999[33]	The Gambia	53% named ≥1 side effect
Howard *et al*, 1981[63]	USA	61% could name 1 side effect	Oduro *et al*, 2008[22]	Ghana	20% knew direct risks
Miller *et al*, 1994[58]	USA	48% named and 86% recognised >1 risk	Pace *et al*, 2005[29]	Uganda	18% named 1 or more side effects
Ravina *et al*, 2010[36]	USA	47% knew which drugs had highest risks, 93% knew PD could get better, worse or not change	Krosin *et al*, 2006[26]	Mali	7% said there were side effects‡
Estey *et al*, 1994[57]	Canada	41% named >1 risk	Kaewpoonsri *et al*, 2006[25]	Thailand	6.6% recalled being told of risks
Van Stuijvenberg *et al*, 1998[53]	The Netherlands	40% knew side effects			
Joffe *et al*, 2001[49]	USA	37% knew research risks			
Penman *et al*, 1984[61]	USA	31% named >3 of 11 risks			
Criscione *et al*, 2003[44]	USA	30% knew there were risks§			
Bergler *et al*, 1980[64]	USA	28% (at start), 3% (3 months later)			
Bergenmar *et al*, 2008[37]	Sweden	18% knew research risks			
Schats *et al*, 2003[47]	The Netherlands	6% knew side effects			

*Arranged from highest to lowest.

†29% did not recall ANY risks of the trial drug, the rest of the participants could name general risks, and at most participants could name up to four specific risks or side effects.

‡The question was complex and multi-choice. The correct answer was the only one that included a mention of side effects. However, it also included information about the potential benefits of the medicine (eg, that it could prevent malaria and correct other health problems).

§But were not asked to name or identify them.

PD, Parkinson's disease.

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Table 5

Understanding of study design and randomisation*

Developed country studies			Developing country studies		
Author	**Country**	**Understood study design**	**Author**	**Country**	**Understood study design**
Van Stuijvenberg *et al*, 1998[53]	The Netherlands	88% placebo design	Moodley *et al*, 2005[27]	South Africa	49% knew they had a 50% chance of receiving placebo; 19% understood placebo
Criscione *et al*, 2003[44]	USA	87% placebo design	Hill *et al*, 2008[23]	Ghana	13% understood 'not all trial capsules were the same'
Howard *et al*, 1981[63]	USA	86% double blind design	Leach *et al*, 1999[33]	The Gambia	10% placebo design†
Harrison *et al*, 1995[55]	USA	79%			
Pope *et al*, 2003[46]	Canada	76% placebo design			
Bergler *et al*, 1980[64]	USA	64% (at start), 28% (3 months later)			
Developed country studies			**Developing country studies**		
Author	**Country**	**Understood randomisation**	**Author**	**Country**	**Understood randomisation**
Ravina *et al*, 2010[36]	USA	90%, yet only 67% understood there was a 1 in 3 chance of receiving placebo	Ellis *et al*, 2010[18]	Mali	80% of adults 90% of parents
Simon *et al*, 2003[48]	USA	68% of majority English speakers	Krosin *et al*, 2006[26]	Mali	68%
		26% of minority English speakers			
		14% of minority non-English speakers			
Bergenmar *et al*, 2008[37]	Sweden	85%	Pace *et al*, 2005[28]	Thailand	31%
Gammelgaard *et al*, 2004[41]	Denmark	79%	Moodley *et al*, 2005[27]	South Africa	21%
Criscione *et al*, 2003[44]	USA	50%	Pace *et al*, 2005[29]	Uganda	19%
Van Stuijvenberg *et al*, 1998[53]	The Netherlands	50%			
Kodish *et al*, 2004[42]	USA	50%			
Howard *et al*, 1981[63]	USA	43%			
Pope *et al*, 2003[46]	Canada	39%			
Benson *et al*, 1985[60]	USA	33% of depression study, 16% of schizophrenia study			
Hietanen *et al*, 2000[51]	Finland	23%			
Schats *et al*, 2003[47]	The Netherlands	22%			

*Arranged from highest to lowest %.

† When broken down into those who had received a written information sheet at least a week before consent, 15% of those who had received the sheet understood that there was a placebo group versus 4% of those who had not received prior written information.

Table 6

Voluntariness: knew could withdraw or refuse*

Developed country studies			Developing country studies		
Author	**Country**	**Knew could withdraw**	**Author**	**Country**	**Knew could withdraw**
Joffe *et al*, 2001[49]	USA	90%; 99% knew could refuse	Ellis *et al*, 2010[18]	Mali	96% of adults 93% of parents
Ellis *et al*, 2010[18]	USA	98%	Karim *et al*, 1998[34]	South Africa	93% of evaluation study group, 88% of sensitisation control group†
Ravina *et al*, 2010[36]	USA	98% felt 'free to refuse to participate'	Pitisuttithum *et al*, 1997[35]	Thailand	88% knew could refuse
Marshall *et al*, 2006[19]	USA	97%	Moodley *et al*, 2005[27]	South Africa	87%
Criscione *et al*, 2003[44]	USA	96%	Pace *et al*, 2005[28]	Thailand	71%
Benson *et al*, 1985[60]	USA	Depression study: 95%; 75% knew could refuse.	Marshall *et al*, 2006[19]	Nigeria	67%
		Schizophrenia study: 83%; 75% knew could refuse	Minnies *et al*, 2008[24]	South Africa	65%
Bergenmar *et al*, 2008[37]	Sweden	93%; 100% knew could refuse	Pace *et al*, 2005[29]	Uganda	65%; 41% knew could refuse
Franck *et al*, 2007[40]	UK	91%	Kaewpoonsri *et al*, 2006[25]	Thailand	53.1%
Van Stuijvenberg *et al*, 1998[53]	The Netherlands	91%	Lynöe *et al*, 2001[32]	Bangladesh	48%: 65% knew could refuse
Lynöe *et al*, 2004[43]	Sweden	90%	Sarkar *et al*, 2009[21]	India	50%
Simon *et al*, 2003[48]	USA	90% of majority English speakers	Ekouevi *et al*, 2004[30]	Côte d'Ivoire	27%
		78% of minority English speakers	Joubert *et al*, 2003[31]	South Africa	24% (but 92% said care would no longer be good if they quit)
		60% of minority non-English speakers	Oduro *et al*, 2008[22]	Ghana	21%
Montgomery *et al*, 1998[52]	UK	83%	Krosin *et al*, 2006[26]	Mali	10%
Penman *et al*, 1984[61]	USA	80%			
Riecken *et al*, 1982[62]	USA	80%; 95% knew could refuse			
ACHRE, 1996[54]	USA	78%			
Bergler *et al*, 1980[64]	USA	77% (at start), 61% (3 months later)			
Harth *et al*, 1995[56]	Australia	45% (but 32% said would not be allowed)			
Schats *et al*, 2003[47]	The Netherlands	25%; 59% knew could refuse‡			

*Arranged from highest to lowest %.

†However, 98% of the evaluation study group and 100% of the sensitisation control group said hospital would not allow them.

‡Knew participation was not obligatory.

ACHRE, Advisory Committee on Human Radiation Experiments.