VOLUME 29 · NUMBER 1 · JANUARY 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

What Oncologists Believe They Said and What Patients Believe They Heard: An Analysis of Phase I Trial Discussions

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Submitted April 27, 2010; accepted September 13, 2010; published online ahead of print at www.jco.org on November 22, 2010.

Supported by Cancer Research United Kingdom Grant No. C54/A7374.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/11/2901-61/$20.00

DOI: 10.1200/JCO.2010.30.0814

ABSTRACT

Purpose
Evaluation of the communication and informed consent process in phase I clinical trial interviews to provide authentic, practice-based content for inclusion in a communication skills training intervention for health care professionals.

Patients and Methods
Seventeen oncologists and 52 patients from five United Kingdom cancer centers consented to recording of phase I trial discussions. Following each consultation, clinicians completed questionnaires indicating areas they felt they had discussed, and researchers conducted semistructured interviews with patients examining their recall and understanding. Patients and oncologists also completed the Life Orientation Test-Revised questionnaire, measuring predisposition toward optimism. Independent researchers coded the consultations identifying discussion of key information areas and how well this was done. Observed levels of agreement were analyzed for each consultation between oncologist-coder, oncologist-patient, and patient-coder pairs.

Results
In several key areas, information was either missing or had been explained but was interpreted incorrectly by patients. Discussion of prognosis was a frequent omission, with patients and coders significantly more likely to agree that oncologists had not discussed it (odds, 4.8; $P < .001$). In contrast, coders and oncologists were more likely to agree that alternate care plans to phase I trial entry had been explained (odds, 2.5; $P = .023$).

Conclusion
These data indicate that fundamental components of communication and information sharing about phase I trial participation are often missing from interviews. Important omissions included discussion of prognosis and ensuring patient understanding about supportive care. These findings will inform educational initiatives to assist communication about phase I trials.

J Clin Oncol 29:61-68. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Handling uncertainty in ill and anxious patients is never easy. Clinicians who had benefited from an evidence-based communication program about phase III randomized clinical trials requested help with early-phase studies.[1] Effective communication about phase I and phase II trials is arguably more difficult than that for phase III trials because it demands a complex amalgam of advanced skills: balancing honesty about likely therapeutic gains versus risks and managing the many emotions evoked.

The primary end points of phase I trials are usually assessment of toxicity and determination of dose and schedule for further study, rather than antitumor effectiveness.[2] Secondary end points usually include pharmacokinetics and pharmacodynamics. Most phase I trials do not convey any therapeutic benefit and carry a risk of adverse effects. Studies reveal that many patients have limited understanding of the primary research aims, unrealistic expectations about benefits and risks, a questionable appreciation of their right to abstain or withdraw, and little knowledge about alternatives to phase I trial participation.[3]

The reasons for these apparent deficiencies in comprehension are unclear and are likely to be multifactorial. Most previous studies rely on uncorroborated accounts or recall of information and understanding; only a few have directly observed actual consultations between doctors and patients and the informed consent process.[4] One study reported that despite provision of complete information about the phase I drug characteristics, the modalities of

treatment, and follow-up to 80% of patients, only 34% were informed about rights to refuse or withdraw without compromising future care.[5] Additional evaluations on a few taped consultations in this study indicated poor checking of comprehension and little appreciation of indirectly expressed needs and anxieties, which hampered participation and cogency of patients' decision making.

In another study,[6] researchers analyzed 29 of 77 phase I audiotapes from 12 oncologists. Patients completed questionnaires, and every third patient was interviewed. Unfortunately, these analyses were reported only in general terms but concluded that oncologists gave mixed messages about the putative benefits of phase I trial participation.

Most interviews with oncologists and patients about phase I trials provide predominantly subjective descriptions of the informed consent process. Evidence suggests that clinicians can be "vague, ambiguous, and indeterminate about benefit, rather than clearly negative"[7]; for example, patients report clinicians' enthusiasm, assurances of good results, and descriptions of drugs as potentially efficacious treatment rather than as an experimental agent.[8]

We examined phase I discussions from three perspectives: (1) what oncologists said (audiotaped and coded), (2) what areas oncologists believed they covered (self-report questionnaire), and (3) what patients recalled and understood about trial participation immediately following the consultation (semi-structured interview). In addition, we measured characteristics of both physicians and patients that might have influenced the communication and its interpretation, including mental health and predisposition toward optimism.

PATIENTS AND METHODS

Patient Sample

Between August 2007 and December 2008, clinicians and patients from five United Kingdom cancer centers in Glasgow, London, Southampton, and Oxford (all in the United Kingdom) provided written informed consent to participate. The study was approved by Oxfordshire Research Ethics Committee C. Sampling from these five centers ensured a representative mix of socioeconomically diverse patient populations and a range of different phase I trials.

Clinicians

Clinicians (consultant oncologists [attendings] and specialist registrars in oncology [residents]) actively involved in early-stage (phase I and phase II) trials completed demographic questionnaires and listed their most challenging phase I communication difficulties. Before their first consultation, they completed the Life Orientation Test-Revised (LOT-R), a standard measure of optimism.[9] Following each consultation, they completed a checklist indicating areas of information they felt they had covered such as whether or not unknown adverse effects were discussed, the voluntary nature of the trial, and other treatment options (Fig 1).

Patients

All patients in attendance for a phase I discussion when researchers were present in clinics were approached and invited to join the study. Those interested read an information sheet and consented to audiotaping of their consultations and interviews with the researchers.

Following the phase I consultation, researchers conducted semi-structured exit interviews with patients. The interviews probed whether or not the key information areas listed in Table 1 had been covered by the oncologists. A qualitative analysis of comments made during the exit interviews will be reported at a later date. Researchers also gave patients three questionnaires to complete at home and return by mail (Fig 1). Questionnaires asked about reasons for decisions (Accept or Decline Trial Questionnaire), psychological well-being (General Health Questionnaire 12 [GHQ-12]),[10] and optimism (LOT-R).[9]

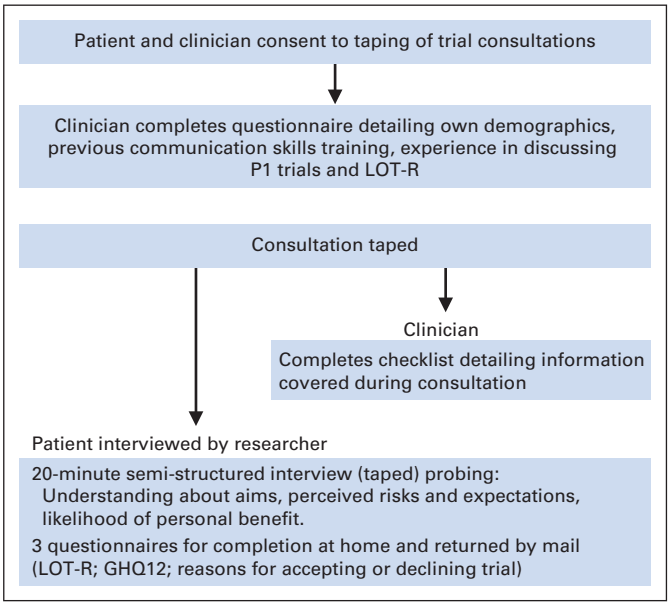

Fig 1. Timing and administration of questionnaires. P1, phase 1; LOT-R, Life Orientation Test-Revised, GHQ12, General Health Questionnaire 12.

Content Analysis

The content of the audiotaped consultations was analyzed by two researchers who used a checklist that identified key information areas covered in both the patients' interviews and in clinicians' postconsultation questionnaire as well as the clinicians' manner of delivery. Important content areas included trial purpose, procedures, and drug(s); associated risks and benefits; right to abstain or withdraw; and alternatives to trial participation. Delivery covered general communication style, language, and jargon. The rate-rerate reliability of the two coders and the inter-coder reliability were examined by using the κ coefficient.

Statistical Analyses

We assessed oncologists' perceptions of whether or not they had addressed issues within the key content categories in Table 1 by measuring the

Table 1. Key Content Issues for Coding the Phase I Consultations

Key Issues
1. Prognosis: Established knowledge about current status or prognosis (If prognosis is mentioned by the patient, this had to be acknowledged and confirmed by the clinician. If no mention was made even after explicit inquiry, then the clinician was required to disclose the prognosis.)
2. Other treatment or care options: Explained treatments for symptomatic relief and standard palliative chemotherapy or radiotherapy options as appropriate
3. Aims of the trial: Outlined aims of the phase I trial (eg, toxicity assessment, dose escalation)
4. Medical benefits: Explained the probable lack of any personal therapeutic benefits
5. Extra effort: Explained the effort required in terms of extra tests, trips to hospital, and so on
6. Unknown adverse effects: Elaborated the risk of unknown adverse effects
7. Voluntary nature: Checked to see whether patient (and family) understood voluntary nature of participation
8. Right to withdraw: Explained the right to withdraw from the trial at any time without giving a reason

agreement between their questionnaire responses postconsultation and the coders' analyses of the audiotapes. For each of the issues, we formulated a binary variable to indicate agreement between coder and clinician (1) or otherwise (0) for each consultation. We then fitted a logistic regression model for this variable to estimate an overall odds of agreement in each area considered. Odds > 1 indicate agreement whereas odds ≤ 1 correspond to poor agreement. Some clinicians interviewed two or more patients; therefore, responses from consultations led by the same clinician may be correlated. We accounted for this correlation through estimation of the odds and their variances by using a generalized estimating equation approach.[11]

We followed a similar procedure to assess patients' perceptions about consultations. Patterns of communication between clinicians and patients that led to agreement or disagreement were examined by modeling the probability of agreement adjusting for putatively influential explanatory variables. When using explanatory variables to predict agreement through a logistic regression, there are risks of estimating spurious effects that are due to chance. This may happen if one (or both) individual(s) has an inclination to answer "yes" more often than "no" to the questions for some categories of the explanatory variables. In this case, even if the individuals were independent, the probability of agreement may still be related to the explanatory variables and therefore be mistakenly interpreted as pure agreement. We addressed this by incorporating corrections for chance agreement in the linear predictor following Lipsitz.[12] These adjustments yield chance-corrected measures of agreement (Appendix, online only).

Levels of optimism were compared between patients, consultant oncologists, and specialist registrars by fitting a linear regression model with LOT-R scores as the dependent variable and group as the explanatory variable to contrast the mean scores. Data from the audiotapes, clinician questionnaires, and patient/researcher interviews and questionnaires were compared to provide (1) objective reports on whether or not key information areas were included in the discussions; (2) effects of clinician communication and other patient and consultation variables on comprehension of trial information, expectations, and decision making; and (3) identification of good and poor practice and factors associated with communication problems.

RESULTS

Audiotape Coding

We examined inter-rater ($\kappa = 0.66$; standard error [SE], 0.046) and rate-rerate ($\kappa = 0.745$; SE, 0.042; and $\kappa = 0.844$; SE, 0.034) reliability for 10% of interviews and found good agreement.

Clinicians

Table 2 summarizes the characteristics of the 17 participating oncologists; 40% were consultants who had more clinical trial experience, including being principal investigators. Most (14 of 17) had received some communication skills training, although this was not specific to clinical trial discussions. The median and mean number of consultations per clinician was three (range, one to eight).

Patients

Fifty-eight of 62 patients approached consented to join the communication study. For the triangulation analysis, a maximum of 52 recordings were used (two recorder errors, two patients were ineligible because they failed phase I screening tests, and two patients withdrew [refused interview]). Fifty percent (26 of 52) had previous phase II or phase III trial experience, and 48% (21 of 44) who completed the GHQ-12 had scores indicating probable psychological morbidity (Table 3).

Table 2. Clinician Characteristics (n = 17)

Characteristic	Consultant Oncologists (n = 7)	Specialist Registrars in Oncology (n = 10)
Sex		
Male	6	7
Female	1	3
Age groups, years		
25-34	1	7
35-44	1	3
45-54	4	
≥ 55	1	
Communication training		
None	2	1
Basic only	0	1
Postgraduate only	1	0
Both basic and postgraduate	4	8
Phase I	3	1
Phase I experience, years		
0-1	0	4
2-5	1	6
6-9	0	0
10-20	5	0
> 20	1	0
No. of phase I patients per month		
1-6	3	2
7-10	1	4
11-15	2	3
16-20	1	0
> 20	0	1
Principal investigator		
Current/previous	6	1
Never	1	9
LOT-R scores		
Mean	19.7*	15.8
Standard deviation	2.9	2.4
Range†	15-23	12-19

Abbreviation: LOT-R, Life Orientation Test-Revised.
*One very low score was treated as an outlier and removed from all of the LOT-R analyses.
†Possible measure range was 0 to 24.

Descriptive Statistics

Table 4 lists the number of times coders heard key information areas discussed during individual clinicians' consultations and for clinicians overall. Of the 17 oncologists in the study, 13 mentioned prognosis in < 50% of their consultations; 10 mentioned unknown adverse effects, nine mentioned the voluntary nature of participation, and 10 mentioned the right to withdraw at any time.

Observer Agreement Ratings

Appendix Table A1 (online only) summarizes the data through contingency tables for each area listed in Table 1. Individual rates of agreement between clinicians and patients are presented in Appendix Table A2 (online only). Figure 2 depicts overall agreement through Bangdiwala's observer agreement figures.[13,14] Each plot shows odds of agreement between clinician and patient, clinician and coder, and patient and coder.

The information areas in which the majority in all three groups were in agreement that the topics had been discussed were establishing

Table 3. Phase I Patient Characteristics

Characteristic	Patients (n = 52) No.	%
Sex		
Male	24	46
Female	28	54
Age, years		
Mean	58.12	
Standard deviation	10.59	
Range	29-76	
Age group, years		
25-34	3	6
35-44	2	4
45-54	13	25
55-64	19	36
≥ 65	15	29
Marital status		
Partner	38	73
No partner	14	27
Employed		
Yes	12	23
No	40	77
Education		
No school examinations	19	36
GCSE, A Level	16	31
University and higher	17	33
Cancer site		
Colorectal/upper GI	24	46
Gynecologic	9	17
Breast	8	15
Skin	5	10
Urologic	2	4
Other	4	8
Previous trial experience		
Phase II or phase III trials	26	50
Type of trial discussion		
General	16	31
Dose escalation study	14	27
Targeting/antibody/immunotherapy	16	31
Combination	6	11
GHQ-12		
Above threshold (≥ 4)	21	48
Below threshold (< 4)	23	52
Missing data	8	
LOT-R scores		
Mean	15.7	
Standard deviation	3.6	
Range	8-24	

Abbreviations: GCSE, General Certificate of Secondary Education; GHQ-12, General Health Questionnaire 12; LOT-R, Life Orientation Test-Revised.

aims of the trial and the extra burdens involved in trial participation. Results for establishing aims of the trial were 88% (44 of 50) clinicians, 86% (43 of 50) patients, and 82% (41 of 50) coders, all of which had significant odds of agreement: 6.1, 3.6, and 4.2, respectively; all $P <$ .001. Results for explaining extra burdens involved in trial participation were 88% (43 of 49) clinicians, 84% (41 of 49) patients, and 84% (42 of 50) coders (odds range, 4 to 7.2; $P \leq .001$).

There were two topics on which clinicians and patients were in agreement that the subject had been discussed compared with the coder: unknown adverse effects (odds, 2.9; $P < .001$) and voluntary nature (odds, 6.2; $P < .001$). In contrast, coders rather than patients were more likely to agree with clinicians that other care or treatment plans (odds, 2.5; $P = .023$), the right to withdraw (odds, 2.9; $P = .013$), and likelihood of medical benefit (odds, 5.1; $P < .001$) were discussed.

The one area in which the coder and the patients were in agreement was in the discussion of prognosis. Fifty percent of doctors (25 of 50) reported discussing it in the consultation, but only 12% of patients (6 of 52) and 20% of coders (10 of 50) agreed that it had been mentioned (odds, 4.8; $P < .001$).

Inspection of clinicians' individual rates of agreement with their patients shows that those clinicians who saw more patients did not have an important influence on the overall agreement of key areas, except right to withdraw in which two clinicians who interviewed 14 patients showed poorer agreement than most of the other doctors (Appendix Table A2).

Effect of Other Variables

We investigated whether factors such as having met the clinician previously and being told about or receiving written information about phase I trials in another consultation influenced the discrepancies reported in the observed agreement plots. Specifically, we examined the influence these had for right to withdraw, voluntary nature, unknown adverse effects, and discussions about prognosis.

Oncologists were 13 times more likely to report having discussed the patient's right to decline participation if the patient had not been under his/her care before (odds ratio, 12.9; 95% CI, 1.87 to 89.21) and 11 times more likely to report having discussed the patient's right to withdraw from the trial if they had seen the patient previously (odds ratio, 11.2; 95% CI, 3.6 to 34.5).

Optimism LOT-R

LOT-R results were available for 16 of 17 clinicians and 45 of 52 patients. Mean scores were 19.7 (standard deviation [SD], 2.9) for the consultant oncologists, 15.8 (SD, 2.4) for specialist registrars, and 15.7 (SD, 3.6) for patients. Linear regression analysis confirmed that differences between patients and consultants and between specialist registrars and consultants were statistically significant ($P = .009$ and $P = .03$, respectively). The consultants were more optimistic than both patients and specialist registrars. However, the degree of optimism did not influence levels of agreement between oncologists and patients on any of the key points.

Patient Interviews

A qualitative descriptive analysis of patients' interviews will be reported separately along with reasons for participating in or declining to enter the trial. However, some quotes in the discussion illustrate apparent inconsistencies between patients' recollection of what was said or how they chose to interpret or maybe ignore oncologists' statements.

DISCUSSION

Previous studies suggested that patients' limited understanding of phase I trial aims and unrealistic expectations about therapeutic benefit occur because of clinicians' poor or ambiguous explanations.[15,16] Many argue that oncologists use terminology that misleads patients into believing the trial drug is already a new treatment, rather than an

Table 4. Coders Record of Whether Discussion of the Key Information Areas Was Heard During the Consultations per Clinician and Summarized

	Prognosis		Other Treatment or Care Options		Aims of the Trial		Medical Benefits		Extra Effort		Unknown Adverse Effects		Voluntary Nature		Right to Withdraw	
Clinician ID	Ratio	%	Ratio	%	Ratio	%	Ratio	%	Ratio	%	Ratio	%	Ratio	%	Ratio	%
1	1/7		1/7		5/7		2/7		6/7		3/7		3/7		0/7	
2	1/8		5/7		7/8		7/8		6/8		4/8		2/8		0/8	
3	0/3		2/3		3/3		2/3		3/3		3/3		3/3		3/3	
4	1/4		2/4		4/4		4/4		4/4		1/4		3/4		2/4	
5	0/1		1/1		1/1		0/1		1/1		0/1		1/1		0/1	
6	0/1		0/1		1/1		1/1		1/1		0/1		1/1		1/1	
7	1/1		0/0		1/1		1/1		1/1		0/1		0/1		0/1	
8	0/4		0/4		2/4		4/4		4/4		1/4		2/4		4/4	
9	1/3		2/3		3/3		3/3		1/3		3/3		2/3		1/3	
10	0/2		0/2		2/2		1/2		1/2		1/2		0/2		0/2	
11	2/2		2/2		2/2		2/2		2/2		2/2		1/2		2/2	
12	1/2		2/2		1/2		1/2		2/2		1/2		0/2		1/2	
13	2/3		2/3		3/3		3/3		3/3		1/3		1/3		2/3	
14	0/2		2/2		1/2		0/2		1/2		0/2		0/2		0/2	
15	0/1		1/1		1/1		1/1		1/1		1/1		1/1		0/1	
16	0/3		2/2		3/3		2/3		3/3		1/3		1/3		1/3	
17	1/5		1/5		3/5		4/5		4/5		2/5		1/5		1/5	
Overall	11/52	21	25/49	51	43/52	83	38/52	73	44/52	85	24/52	46	22/52	42	18/52	35

NOTE. In each ratio, the numerator indicates the number of consultations in which the information was heard, and the denominator represents the number of consultations led by the clinician.
Abbreviation: ID, identification.

experimental agent, thus creating therapeutic misconceptions. The trial discussions in our study were taped, so results from our content analyses, together with questionnaires and postconsultation interview data show that what clinicians say and what patients hear or interpret can be two different things. In addition, optimistic predispositions of both parties may influence discussion and interpretation.

Our most disappointing finding was the frequent omission of checking understanding about prognosis, which we believe is a fundamental and ethical prerequisite for patients' being able to consider how best to use the time left to them. We used broad criteria for measuring this, which included confirmation of prognostic information volunteered by patients following a general inquiry about their current disease status or an explicit inquiry and disclosure if patients seemed unclear. Discussing prognosis is undoubtedly a difficult task influenced by many factors, including patients' hope and cultural background; however, others have recommended that patients contemplating early-phase trials should have a clear understanding of their situation to enable truly informed consent and that it is not reasonable for clinicians to opt out of these discussions.[17]

Some patients appeared nihilistic about palliative care, preferring not to acknowledge that alternatives to the experimental drug had been discussed. Our findings fit with suggestions by Miller and Joffe[18] that many patients considering early-phase trials are "therapeutic optimists" who, despite being aware of both prognosis and the experimental nature of the trial drug(s), maintain hopes for personal benefit. There may be psychological advantages to this stance: a study of patients participating in a phase IB trial showed that high levels of treatment-specific optimism were associated with better mental health outcomes at both the beginning and end of treatment.[19]

Comments made by patients we interviewed reflected the hope they attached to trial participation. When asked "If you take part in this trial, do you think you would benefit medically or not?" many articulated hopeful outcomes, even though recordings showed that oncologists had been explicit that the phase I trial was unlikely to convey benefit. For example: "I like to think positively that it's all for my benefit and in the long-term, it will prolong my life. Something's happening—I'm doing something."

If clinicians were even slightly ambiguous, then optimistic interpretations ensued. For example, "For me, he said they had absolutely no idea whether it would be beneficial or not, but if it's not, we haven't lost anything, and if it is, then we have gained something."

Similarly, when asked if trial aims had been explained, some patients revealed disturbing misinterpretations or hopeful elaborations: "He's tried this treatment on laboratory animals and he now wants to try it on humans; incidentally, it may cure my cancer." Patients' hopes may change in the transition from curative to palliative care. Clinicians need specific skills to maintain honesty about poor prognoses while helping patients to maintain hope through realistic goal setting.[20]

Another observation in our study was that patients who had previously received treatment from the oncologists discussing the phase I trial were more likely to claim that the voluntary nature of the trial and right to withdraw were discussed during the recorded consultation, even though the coders reported it in $< 50\%$ of trial discussions. Because these patients were also more likely to have participated in previous clinical trials and/or been given information about the phase I trial, they might have brought this prior knowledge to the consultation and "heard" it expressed although it was absent.

Patient-centered interventions have demonstrated a benefit to patient understanding of phase I trials at both the informed consent stage[21] and at trial end.[22] However, there is a dearth of research involving clinician-centered interventions and the effect that specific

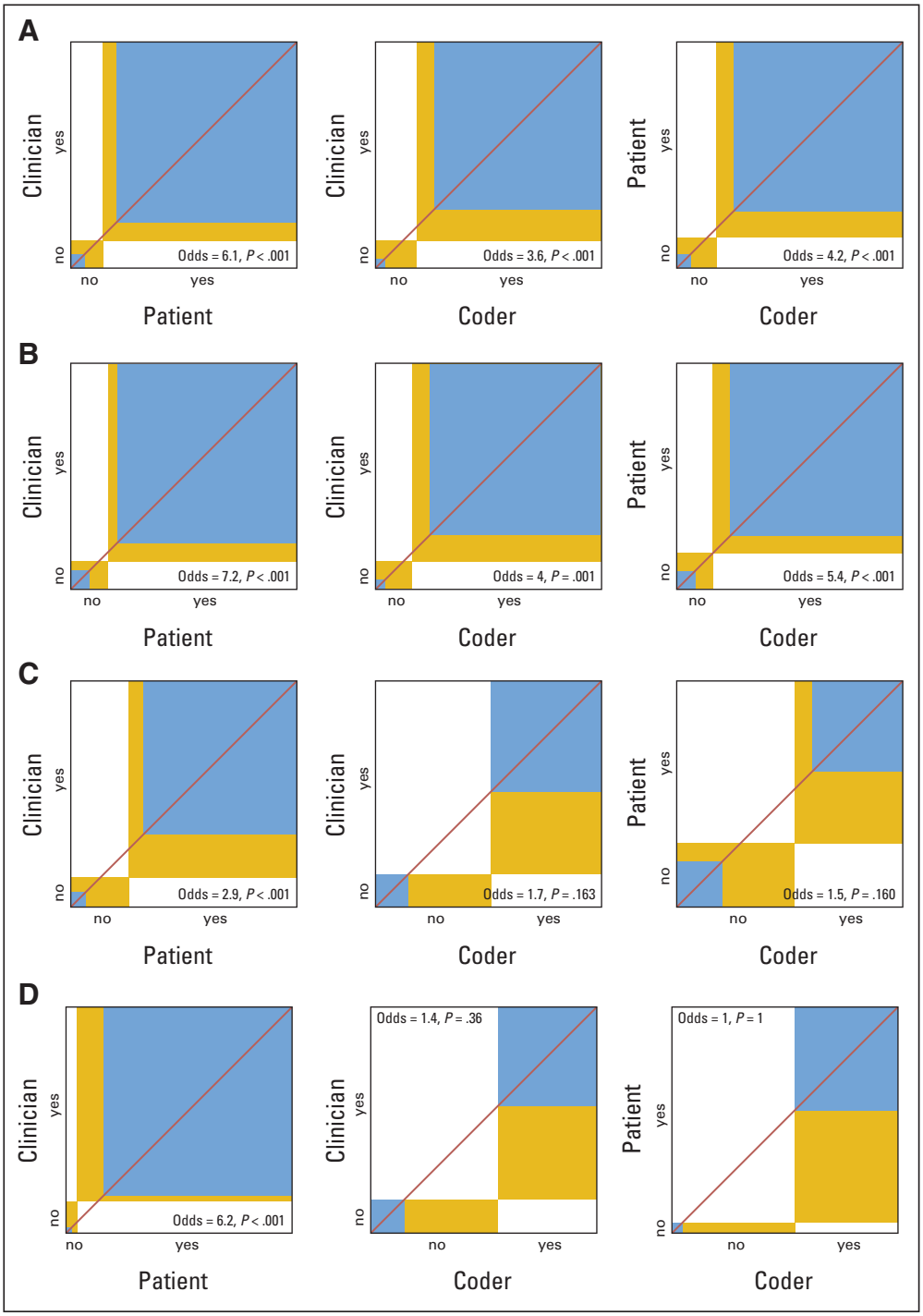

Fig 2. Bangdiwala agreement charts. The extent of agreement (to both "yes" and "no") is represented in these charts by the size of the blue boxes inside gold rectangles located in the diagonal of the plot. Larger blue boxes indicate better agreement, with the larger gold rectangles showing the maximum possible agreement, given the totals of "yes" and "no" responses observed from each individual. Specifically, the bottom left box of the plot depicts agreement between individuals for responses of "no" (ie, the matter was not discussed) whereas the top right box depicts agreement for a "yes," (ie, both parties thought the issue was discussed). The *x* axis and *y* axis give a visual representation of the individuals' inclination to respond "yes" or "no" to the question in turn. Bangdiwala plots are provided for all the key information areas. Each plot shows odds of agreement between clinician-patient, clinician-coder and patient-coder. (A) Establishing aims of phase I trials, (B) extra effort explained, (C) unknown adverse effects, (D) voluntary nature explained, (E) symptomatic care or other treatment plans, (F) possibility of withdrawing, (G) likelihood of medical benefits, and (H) prognosis.

communication training could have on assisting patient understanding of phase I trial information. As novel cancer therapies become more diverse, phase I clinical trial design has become increasingly sophisticated. Trials often incorporate procedures to confirm molecular proof of concept, serial tumor sampling, and biomarker studies, and they often involve combinations of agents. There is therefore an increasing need for health care professionals to have the necessary skills to be able to share complex information that is patient-centered, supports patients' needs in a manner that can be assimilated easily, includes all elements necessary for informed consent, and is compliant with regulatory requirements. Some might feel that the doctor's role is to outline the phase I trial and provide more written information for the patient to assimilate later. Unfortunately, many of these patient information sheets are written in an obscure, jargon-laden manner, hindering rather than assisting comprehension.[23]

Phase I and phase II trials are a vital, integral part of developing, and then implementing within the clinic, novel efficacious therapies. The patients who volunteer to help with this deserve respect and

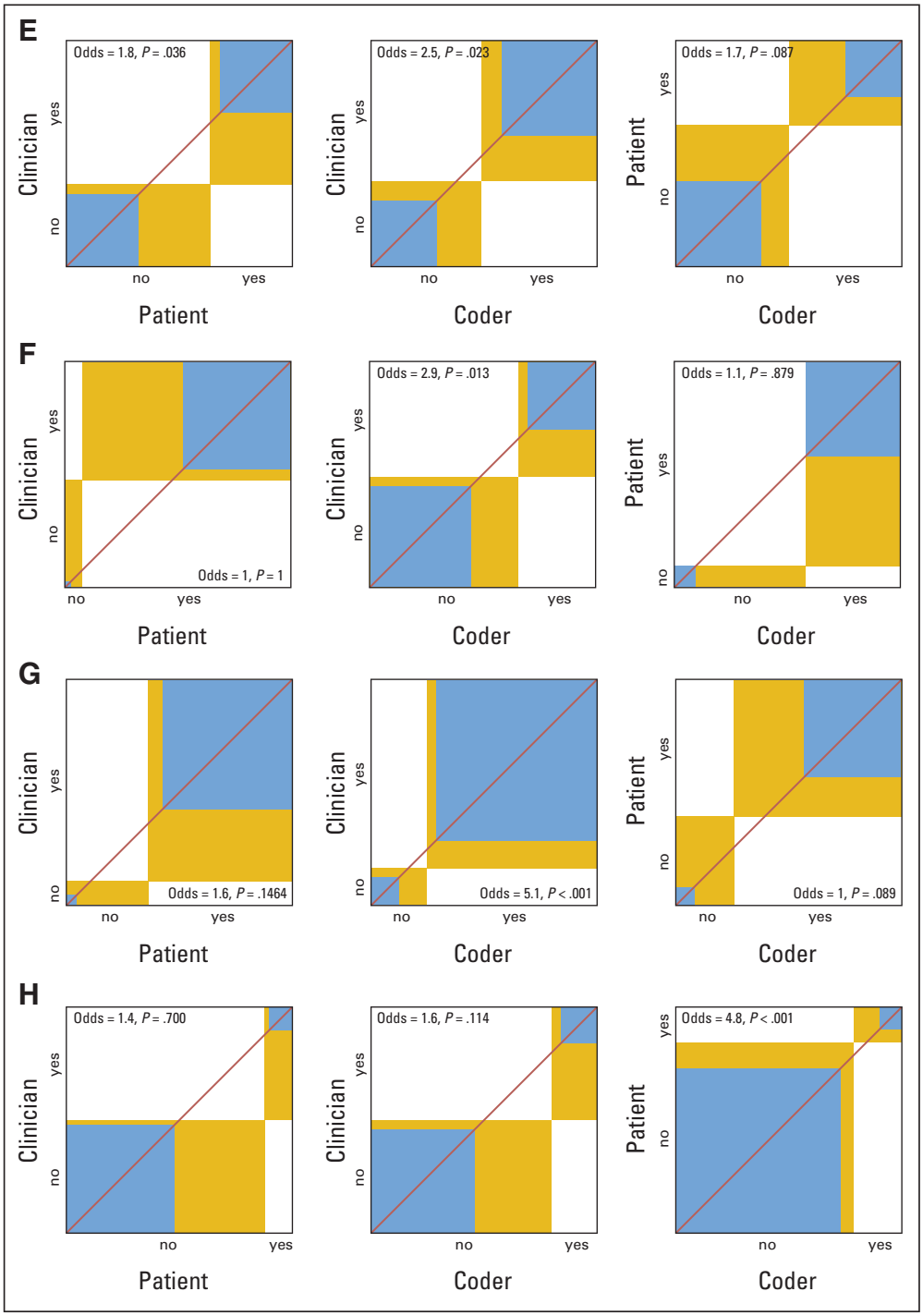

Fig 2. (continued)

clarity delivered supportively and empathetically. Oncologists also need help to achieve this through well-designed training grounded in practice-based evidence.

The triangular analysis of the specific communication problems and difficulties leading to misunderstanding or interpretation identified in this study has been invaluable for development of educational initiatives. The authors are currently evaluating a specific training package for health professionals engaged in discussions about early-phase trials. This comprehensive educational program comprises facilitated discussions using DVDs with illustrative early-phase trial scenarios, didactic evidence-based presentations, and communication exercises. The aim is to improve health professionals' confidence and competence when discussing transitions from conventional treatment to experimental trials. Improvements might mean that more patients would be approached about possible trial entry and that receipt of clearer, more

understandable information would permit more educated decision making about trial entry. Before launching a national training program, we are conducting an evaluation of the program's efficacy and acceptability with health professionals actively engaged in trial recruitment within the United Kingdom. Our educational package is based on a previous design shown to improve phase III communication.[1]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Valerie Jenkins, Lesley J. Fallowfield
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Provision of study materials or patients: Denis C. Talbot
Collection and assembly of data: Valerie Jenkins, Carolyn Langridge, Susan Catt
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