

# Papers

## Fate of biomedical research protocols and publication bias in France: retrospective cohort study

Evelyne Decullier, Véronique Lhéritier, François Chapuis

### Abstract

**Objectives** To describe the fate of protocols approved by the French research ethics committees, a national system created by the French 1988 Huriet-Sérusclat Act; to assess publication bias at a national level.

**Design** Retrospective cohort study.

**Setting** Representative sample of 25/48 French research ethics committees in 1994.

**Protocols** 649 research protocols approved by committees, with follow-up information.

**Main outcome measures** Protocols' initial characteristics (design, study size, investigator) abstracted from committees' archives; follow-up information (rates of initiation, completion, and publication) obtained from mailed questionnaire to principal investigators.

**Results** Completed questionnaires were available for 649/976 (69%) protocols. Of these, 581 (90%) studies were initiated, 501/581 (86%) were completed, and 190/501 (38%) were published. Studies with confirmatory results were more likely to be published as scientific papers than were studies with inconclusive results (adjusted odds ratio 4.59, 95% confidence interval 2.21 to 9.54). Moreover, studies with confirmatory results were published more quickly than studies with inconclusive results (hazard ratio 2.48, 1.36 to 4.55).

**Conclusion** At a national level, too many research studies are not completed, and among those completed too many are not published. We suggest capitalising on research ethics committees to register and follow all authorised research on human participants on a systematic and prospective basis.

### Introduction

Biomedical research protocols, once approved by a research ethics committee, do not have one typical fate. Some protocols have a linear course—approval, initiation, completion, and publication—whereas others may fail at any step. Information about the fate of studies is useful for funders, society, the scientific community, and patients.<sup>1,2</sup> Whether publication is influenced by characteristics of the study such as the direction and strength of findings is of particular interest. Publication bias—defined as the tendency on the parts of investigators, editors, and others to favour publication of research with confirmatory results over research with inconclusive or invalidating results<sup>3</sup>—threatens the reliability of reviews focusing on the published literature.<sup>4</sup>

Four papers have reported on follow-up of protocols approved by research ethics committees: in Barcelona, Oxford, Sydney, and Baltimore.<sup>5-8</sup> In these studies, 79-93% of approved

protocols were initiated and 64-74% of the initiated studies proceeded to completion. Two other studies have reported on follow-up of trials funded by the US National Institutes of Health.<sup>9,10</sup>

Three of the studies based on research ethics committees also assessed publication bias and showed that confirmatory results are associated with publication.<sup>6-8</sup> Odds ratios were highly consistent, ranging from 2.32 to 2.93, and main reason for non-publication was that investigators considered their results not interesting. A survey of authors publishing in psychology in 1973 showed that in the case of statistically non-significant results, the probability of submission was only 6%.<sup>11</sup>

In France, the 1988 Huriet-Sérusclat Act created a national system of 48 research ethics committees (committees for protection of human beings involved in biomedical research), which contribute to a national confederation of research ethics committees.<sup>12</sup> Every protocol involving humans in France must be approved by one of the French committees. The network of structured committees provides prospective and exhaustive recording, but this information had not previously been used for research purposes. Our objective was to describe the fate of clinical protocols after approval and to assess publication bias.

### Methods

We surveyed a sample of 25/48 (54%) committees, randomly chosen to ensure a geographical cross section representative of the French administrative areas (the number of committees in each area depends on population size). All invited committees agreed to participate in the study. We assessed three main outcomes: study initiation, study completion, and publication as a scientific paper (table 1). Our main hypothesis was that studies with confirmatory results were more likely to be published than those either inconclusive or invalidating results. All protocols newly approved between 1 January 1994 and 31 December 1994 by any of the 25 participating French committees were eligible.

### Definitions

We refer to "protocols" up until the time of initiation, from which time we refer to "studies." We collected data either from the committee files or from questionnaires mailed to the principal investigator. We classified study results as "confirmatory," "invalidating," or "inconclusive" (table 1). When the investigator did not respond to questions about publication status, we considered this as missing data.

We classified studies published in formats other than scientific papers as "grey literature"—that is, not generally accessible through libraries (internal reports, theses, abstracts, posters).<sup>13</sup> We classified as "confidential" protocols describing

**Table 1** Data collected for analysis

Data item collected	Categories	Place of collection*
<b>Legal information</b>		
Investigator	Professor, assistant, other	C
Sponsor (administrative and legal responsibility)	Industry, government, other	C
Date of approval	Month and year of protocol approval by committee	C
Revision	No, yes (modifications requested by committee before approval)	C
<b>Study characteristics</b>		
Direct benefit	Without direct individual benefit: none of the participants could expect any individual and immediate benefit (for example, research in physiology or phase I studies are typically considered as studies with no therapeutic benefit); with direct individual benefit: participants can potentially expect a therapeutic benefit from the research	C
Study design	Experimental or non-experimental (descriptive, observational)	C
Study phase	Phase I studies or others (including descriptive studies)	C
No of centres	Single centre or multicentre (multicentre protocols have to be evaluated by the committee of the principal investigator's area)	C/I
Scope of recruitment	National or international	C
Sample size	≤20 patients, 21-50, 51-150, >150	C (planned); I (actual)
Study duration	<2 months, 2-5, 6-18, >18	C (planned); I (actual)
Study topic	Drug testing, cosmetics, medical device, surgical and diagnostic procedures, physiology, others	C
Study design	Descriptive/observational, experimental (non-randomised, randomised + no blinding, randomised + single blinding (patient only), randomised + double blinding (patient and investigator))	C
Funding	No funding, private, public, mixed (private and public)	I
Person writing the protocol	Investigator, sponsor, both	I
<b>Follow-up information</b>		
Adverse effects observed	Yes, no	I
Interim analysis	Interim analysis or no interim analysis	C (planned); I (actual)
Initiation	Initiated or not initiated	I
Reason not initiated		I
Completion	Completed (all patients have to be included and followed as planned) or not completed (including ongoing)	I
Reasons never completed		I
Direction of results	Investigator had to classify their study globally: no hypothesis tested, results confirming study hypothesis ("confirmatory results"), results invalidating study hypothesis ("invalidating results"), results not confirming or invalidating study hypothesis ("inconclusive results")	I
Publication/scientific paper	Published or not published as a scientific paper (study declared by investigator as published in a general or specialised peer-reviewed journal)	I
Date of publication:	Month and year of first results publication as a scientific paper	I
Multiple publication	No, yes (study results leading to more than one scientific paper)	I

Data item collected	Categories	Place of collection*
Language of publication	French only, English only, both	I
Scope of journal of publication	Publishing in French in France or in English (as declared by investigator)	I
Reason for not publishing as scientific paper		I
Dissemination of results (including grey literature)	Oral presentation, internal report, book chapter, thesis/abstract	I

\*C=abstracted from committee's files; I=investigator's answer to mailed questionnaire.

research that the investigator reported was not intended to be published.

### Data collection

Research assistants attended a formal training session on abstraction of study characteristics in June 2000. We assigned an identification number to each protocol to ensure anonymity of the investigator, and completed forms were sent to the coordinating centre.

Research assistants were also locally responsible for obtaining follow-up data from the principal investigator of each protocol by using a mailed questionnaire. In the case of non-response, principal investigators were contacted up to six times by mail or phone. When no answer could be obtained, the local committee contacted the sponsor in summer 2002. When no follow-up response was obtained at all, we classified the reason (refusal, investigator retired, deceased, moved away).

### Ethical considerations

We conducted this study according to the French law on epidemiological and descriptive studies. We collected data anonymously, and no consent was needed as we retrieved no individual information. For research confidentiality, we assigned an identification number and the researchers' names were not mentioned. Therefore, we did not check publication status on any bibliographic database.

### Statistical methods

We obtained frequency distributions for all variables (means, percentages, and 95% confidence intervals). When assessment of association was needed, we used  $\chi^2$  tests.

To build explicative models for the three outcomes (initiation, completion, and publication), we introduced variables significant at the 0.25 level in univariate analysis in a forward stepwise logistic regression (P value for entry = 0.25, P value for remaining = 0.15).<sup>14</sup> We restricted analysis of publication to the cohort of completed studies. We excluded studies from the analysis when their results were not known by the investigator and when they were declared to be not aimed at publication (confidential results or phase I studies).

We calculated the time between the date of approval by the committee and the date of first publication and did a Kaplan-Meier survival analysis.<sup>15</sup> We used a log-rank test to compare survival curves. We excluded studies with an unknown date of first publication. We censored unpublished studies at the date when the questionnaire was completed; we analysed studies described as "in press" as if published at the date of the completion of the questionnaire. We used a Cox univariate analysis to obtain hazard ratios.<sup>16</sup>

We used SAS software for all analyses. We considered associations to be statistically significant when P values were less than 0.05.

**Table 2** Characteristics of 649 protocols, by status at follow-up. Values are numbers (percentages)

	Total (n=649)	Not initiated (n=68)	Ongoing (n=16)	Never completed (n=64)	Completed (n=501)	Published (n=190)
<b>Study topic</b>						
Drug testing	444 (68)	42 (62)	7 (44)	50 (78)	345 (69)	114 (60)
Cosmetics, nutrition	43 (7)	3 (4)	0	0	40 (8)	6 (3)
Medical device testing	35 (5)	6 (9)	1 (6)	0	28 (6)	12 (6)
Surgical and diagnostic procedures	32 (5)	6 (9)	2 (12)	6 (9)	18 (4)	13 (7)
Physiology	48 (7)	4 (6)	3 (19)	2 (3)	39 (8)	24 (13)
Other	47 (7)	7 (10)	3 (19)	6 (9)	31 (6)	21 (11)
<b>Design</b>						
Descriptive or observational study	91 (14)	12 (18)	4 (25)	9 (14)	66 (13)	37 (19)
Experimental study:	558 (86)	56 (82)	12 (75)	55 (86)	435 (87)	153 (81)
Non-randomised	213 (38)	22 (39)	4 (33)	21 (38)	166 (38)	63 (41)
Randomised, no blinding	80 (14)	6 (11)	2 (17)	12 (22)	60 (14)	21 (14)
Randomised, single blinding	70 (13)	8 (14)	2 (17)	8 (15)	52 (12)	11 (7)
Randomised, double blinding	195 (35)	20 (36)	4 (33)	14 (25)	157 (36)	58 (38)
<b>Funding</b>						
No funding	54 (8)	14 (21)	1 (6)	8 (13)	31 (6)	13 (7)
Private funding	471 (73)	46 (68)	7 (44)	42 (66)	376 (75)	113 (59)
Public funding	82 (13)	7 (10)	4 (25)	8 (13)	63 (13)	46 (24)
Mixed funding	42 (6)	1 (1)	4 (25)	6 (9)	31 (6)	18 (9)
<b>Single v multicentre, scope</b>						
National:	530 (82)	62 (91)	12 (75)	46 (72)	410 (82)	140 (74)
Single centre	358 (68)	43 (69)	3 (25)	21 (46)	291 (71)	89 (64)
Multicentre	172 (32)	19 (31)	9 (75)	25 (54)	119 (29)	51 (36)
International multicentre	119 (18)	6 (9)	4 (25)	18 (28)	91 (18)	50 (26)
<b>Planned sample size</b>						
≤20 patients	221 (34)	24 (35)	2 (13)	17 (27)	178 (36)	61 (32)
21-50 patients	177 (27)	19 (28)	4 (25)	23 (36)	131 (26)	43 (23)
51-150 patients	107 (17)	15 (22)	1 (6)	11 (17)	80 (16)	34 (18)
>150	137 (21)	10 (15)	9 (56)	12 (19)	106 (21)	48 (25)
Not available	7 (1)	0	0	1 (1)	6 (1)	4 (2)
<b>Planned duration</b>						
<2 months	94 (14)	5 (7)	0	5 (8)	84 (17)	7 (4)
2-5 months	105 (16)	7 (10)	1 (6)	5 (8)	92 (18)	25 (13)
6-18 months	160 (25)	19 (28)	4 (25)	21 (33)	116 (23)	65 (34)
>18 months	113 (17)	12 (18)	8 (50)	16 (25)	77 (15)	44 (23)
Not available	177 (27)	25 (37)	3 (19)	17 (27)	132 (26)	49 (26)

## Results

In 1994 the 25 committees evaluated a total of 1143 protocols. We did not include protocols that were approved in 1993 (n = 19, 2%) or 1995 (n = 82, 7%), that were dropped by the investigator before formal approval (n = 48, 4%), or for which committee submission was not required by the law (n = 12, 1%). Among the 982 protocols included, initial characteristics (available on request) were fully described for 976 (99.4%) protocols.

We did not receive investigators' follow-up answers to the mailed questionnaire for 305 (31%), and 22 (2%) were not suitable for statistical analysis (empty questionnaires or empty pages). This left 649 approved protocols to be included.

### Study of non-responses

Seventeen volunteer committees provided complementary information on reasons for investigator's non-response and gathered data for 185/305 studies (61% of non-respondents). The reasons were refusal to fill in a follow-up form (n = 74, 40%), unable to find the original file (n = 56, 30%), and investigator not located because he or she had moved (n = 42, 23%) or had retired or died and nobody could locate the protocol archives (n = 13, 7%).

Protocols with missing follow-up data (n = 305) did not differ from the included protocols (n = 649) by either type of sponsor or study design, but they more often needed modifications to

gain approval (relative risk 1.25, 95% confidence interval 1.01 to 1.55), were more often multicentre (2.04, 1.66 to 2.50), and were more often international (1.45, 1.18 to 1.78).

### Characteristics of approved protocols

The most common characteristics of the 649 approved protocols were drug testing topic (68%), private funding (73%), and conducted nationally only (82%) (table 2). Experimental designs were most frequent, and 62% of them were randomised. Planned study size was less than 20 patients in 34% of studies, and expected duration of study was less than 18 months in 56% of the studies

### Fate of approved protocols

Figure 1 shows the fate of biomedical research protocols for the three study outcomes. Ninety per cent (581/649) of approved protocols were initiated at the time of our study, and 86% (501/581) of these were completed. Protocols not initiated tended more often to be national (91% v 82%), to be testing medical devices (9% v 5%), and to have no funding (21% v 8%) (table 2).

### Initiation of protocols

Table 3 shows the factors associated with study initiation. Phase I protocols were about three times more likely to begin than others. Protocols with mixed funding were also most likely to be initiated, as were multinational ones.

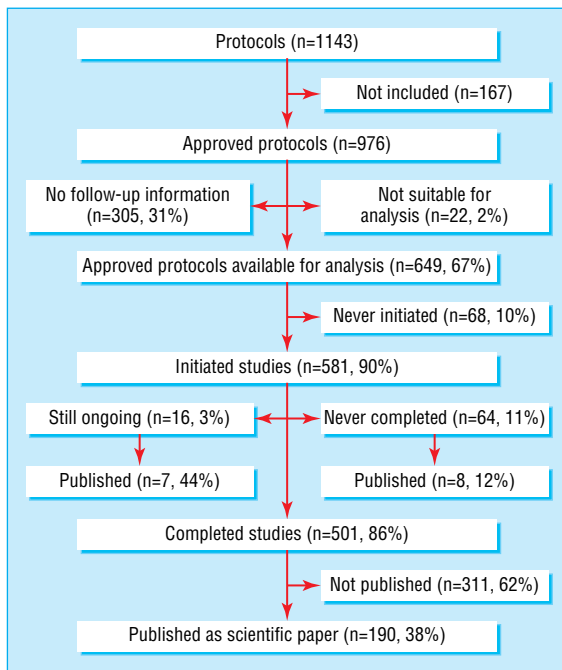


Fig 1 Fate of biomedical research protocols

Among the 68 (10%) protocols that were not initiated, reasons given for non-initiation were refusal of the legal sponsor (n = 21, 31%), problems with recruitment of patients (n = 15, 22%), technical aspects and feasibility (n = 9, 13%), absence of funding (n = 8, 12%), decision of the investigator (n = 8, 12%),

and a similar study having been published (n = 2, 3%). No reason was given for five studies (7%).

**Completion of studies**

Among the 581 protocols initiated, 16 were ongoing. We found in the logistic regression that phase I studies and studies without adverse effects were more likely to be completed (table 3). Investigators gave several reasons for stopping 64 studies before their planned completion, including patient recruitment problems (n = 28, 44%), results found in the interim analysis (n = 13, 20%), incidence of adverse effects (n = 8, 12%), sponsor’s decision (n = 8; 13%), and other (n = 7; 11%).

**Publication of results**

Results were published in a scientific paper for 190/501 (38%) of completed studies, for 7/16 (44%) of ongoing studies, and for 8/64 (12%) of stopped studies. Among stopped studies, publication rates varied from 0% for studies with recruitment difficulties to 3/8 (37%) for studies with adverse events. Among the 501 completed studies, the publication rate was also heterogeneous; it was lower for the subgroup of phase I studies—21/127 (17%) compared with 169/374 (45%) for others.

**Publication bias**

Among the 501 completed studies, 127 (25%) phase I studies and 54 (11%) other studies were deemed confidential and were not included in our analyses of publication bias. We also excluded those protocols in which no hypothesis was tested (n = 32) and those for which the investigator did not know the study results (n = 20) or did not provide information about the direction of results (n = 8) or whether the results were published (n = 12). Thus 248 completed studies were included.

Table 3 Multivariate analysis of study initiation, completion, and publication\*

Study characteristics	Study initiation (n=649)		Study completion (n= 565)		Study publication (n=248)	
	No	Odds ratio (95% CI)†	No	Odds ratio (95% CI)‡	No	Odds ratio (95% CI)§
Type of study:						
Others	509	1.0	432	1.0		NA
Phase I	140	3.09 (1.35 to 7.06)	133	3.30 (1.34 to 7.84)		
Funding:						
None	54	1.0	39	¶	21	¶
Mixed	42	13.70 (1.71 to 109.76)	37		21	
Private	471	2.56 (1.28 to 5.14)	418		167	
Public	82	4.05 (1.50 to 10.94)	71		39	
Adverse events:						
None		NA	448	1.0	194	¶
Adverse effects observed			117	0.52 (0.29 to 0.94)	54	
Results:						
Inconclusive results		NA		NA	44	1.0
Confirmatory results					188	4.59 (2.21 to 9.54)
Invalidating results					16	0.44 (0.10 to 1.86)
Scope:						
National	530	1.0	312	¶	182	1.0
Multinational	119	3.07 (1.27 to 7.40)	253		66	2.25 (1.14 to 4.41)
Design:						
Experimental	558	¶	490	¶	212	1.0
Non-experimental (descriptive/observational)	91		75		36	2.83 (1.13 to 7.06)
Analysis:						
No interim analysis	495	¶	487	¶	203	1.0
Interim analysis	86		78		45	2.21 (0.98 to 4.95)

NA=not applicable (when testing a variable was a nonsense—for example, adverse effect could never explain initiation of a study as it occurs after initiation).  
 \*Adjusted by using forward stepwise regression on the subset of variables linked at the 0.25 level with each criterion; odds ratio of 1.00 assigned to reference category.  
 †Variables tested: sponsor status, investigator status, revision (yes/no), planned duration, scope of recruitment (national/international), funding, phase (phase I/others, including observational), design (experimental v non-experimental).  
 ‡Variables tested: sponsor status, investigator status, revision (yes/no), planned duration, interim analysis, funding, phase (phase I/others), design (experimental v non-experimental), adverse effects.  
 §Variables tested: interim analysis, design (experimental v non-experimental), with or without direct benefit for patient, scope of recruitment (national/international), results.  
 ¶Not included in final model because multivariate statistical significance was >0.25 to enter or >0.15 to stay.

**Table 4** Reasons given by investigators for not publishing (n=102)

Reason	No (%)
Negative results	27 (26)
Writing or submission in progress	23 (23)
Published in other forms	23 (23)
Paper rejected	5 (5)
Other reasons	17 (17)
Not available	7 (7)

Four variables remained in the final model (table 3): direction of results, international versus national scope of the study, study design, and presence of an interim analysis. The stepwise regression confirmed the existence of publication bias; studies with confirmatory results were significantly more likely to be published (odds ratio 4.59, 95% confidence interval 2.21 to 9.54).

### Investigators' reasons for non-publication

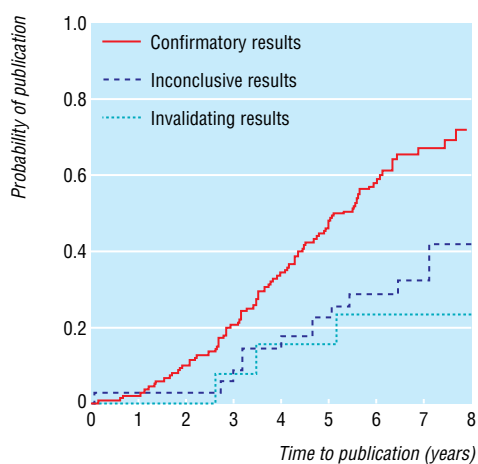
The main reason for non-publication given by the investigator was invalidating results (table 4). Some studies had manuscripts still in the writing or submission stage. Rejection of manuscript was cited for only 5% of unpublished studies. The reasons given by the investigator for non-publication corroborate the logistic regression results (confirmatory results were the strongest predictor of publication).

### Delayed publication of invalidating results

We estimated the effect of direction of results on time to publication for the 248 completed studies. For this analysis, we excluded 61 more protocols because of missing date of first publication. Mean time to publication was significantly associated with direction of results ( $P < 0.001$ ; fig 2): 5.2 years (n=139, 95% confidence interval 4.8 to 5.6) for confirmatory results compared with 6.9 years (n=13; 5.9 to 7.9) for invalidating results, and 6.5 years (n=35, 5.8 to 7.2) for inconclusive results. Cox univariate analysis yielded hazard ratios of 2.48 (1.36 to 4.55) for confirmatory results versus inconclusive results and 0.64 (0.18 to 2.27) for invalidating results versus inconclusive results.

### Dissemination of results

Among the 248 protocols used for the analysis of publication bias, 146 (59%) led to scientific papers. Only 26% of these resulted in more than one paper (table 5), and 92% of studies with multiple publications had confirmatory results. However,



Confirmatory results	139	136	125	110	91	73	52	19	17
Inconclusive results	35	34	34	32	30	27	24	7	6
Invalidating results	13	13	13	12	11	11	9	3	3

**Fig 2** Time elapsed to publication**Table 5** Reporting of 248 completed studies

	No (%)
<b>Studies published as scientific paper (n=146)</b>	
Multiple publication:	
No	108 (74)
Yes	38 (26)
Language:	
English only	109 (75)
French only	13 (9)
English and French	24 (16)
Scope of journal:	
International only	115 (79)
National only	14 (10)
Both	17 (12)
<b>Studies not published as scientific paper (n=102)</b>	
Oral presentation only	13 (13)
No publication or presentation	40 (39)
Reported in grey literature only:	
Internal report	26 (53)
Abstract	6 (12)
Thesis	4 (8)
Internal report plus thesis	4 (8)
Internal report plus abstract	3 (6)
Other (such as book chapter)	6 (12)

the association between multiple publication and direction of results was not significant.

Ninety one per cent of studies were reported to be published in international journals. Moreover, 55% of the studies reported in scientific papers were also presented orally. The 102 remaining studies were not published as scientific papers. Forty (39%) resulted in neither publication nor oral presentation, 13 (13%) resulted in an oral presentation only, 23 (23%) appeared in the grey literature only, and 26 (25%) were reported in both an oral presentation and the grey literature. In total, 49 (48%) studies resulted at least in grey literature (table 5).

## Discussion

Only 38% of completed studies were published. We found evidence for publication bias, favouring publication of confirmatory results (odds ratio 4.59, 95% confidence interval 2.21 to 9.54). The data collected also showed that 90% of approved protocols were initiated, and 86% of these were completed. Such information has been unavailable until now for interventional research conducted on humans and contributes to the literature on publication bias. Previous studies used similar methods: retrospective cohort of protocols approved by a research ethics committee, with a follow-up questionnaire to the investigator,<sup>6-8 17</sup> but focused on one or two local committees, whereas we collected data on a sample of half the committees over a whole country. This may explain the lower publication rate seen in our study. Moreover, we added information on major steps in a protocol's life—from approval and initiation to completion and publication. Phase I studies were more likely to be initiated and completed than were others, probably because they are shorter and smaller.

### Publication bias

The estimated odds ratio for the association between results and publication in our study was similar to, although higher than, those found in the other studies (range 2.32-2.93). This may be because our study population included 22% descriptive non-experimental protocols, which may be easier to do and more likely to be published. We also excluded the stopped studies and those considered to be confidential, which are less likely

### What is already known on this topic

Three observational studies have shown evidence of publication bias in biomedical research approved by research ethics committees, but all were done at a local level

### What this study adds

The fate of biomedical research, from acceptance to publication, has been shown at a national level

Publication bias has been confirmed; confirmatory results were 4.59 times more likely to be published than inconclusive results

to be published. The combined effect is toward the null hypothesis; the true odds ratio is therefore at least as high as the estimated odds ratio. Investigators' decisions to declare a study as confidential were not linked to invalidating or inconclusive results: among non-phase I studies for which direction of results was known ( $n=292$ ) results were confirmatory for 36/40 (90%) confidential studies and 190/252 (75%) non-confidential studies. In our study, the leading reason declared for failure to publish was that the investigator did not find the results interesting (26%), and this is similar to other studies (range 27-43%).<sup>7 9 17</sup> We also found that only 5% of studies were not published because of rejection by a journal, again similar to the findings of other studies (range 5-10%).

Another kind of bias linked to statistical significance was recently reported in a follow-up of randomised controlled trials approved by two Danish research ethics committees<sup>18</sup>: investigators were more likely to report statistically significant outcomes and failed to report others (outcome reporting bias). The reasons given were similar to those explaining non-publication: 30% were not reported owing to the lack of statistical significance.

### Non-response

The major limitation of our study was the non-response rate (31%), which was similar to those of other studies (range 22-30%),<sup>7 8 17</sup> confirming how difficult it is to obtain answers from investigators, especially in a nationwide survey. In our study, the characteristics of protocols lost to follow-up were similar to those never initiated (multicentre and international studies). Non-response may thus be associated with never initiated protocols.

### Registering trials

As publication bias is a major problem for science and for any type of review of available knowledge, we strongly support prospective registration of protocols—proposed in 1986 and supported by many authors<sup>4 19 20</sup>—for example, with a unique protocol identifier. In 1999 the editors of the *BMJ* and the *Lancet* affirmed the need to create a trial registry.<sup>21</sup> In 2004 the International Committee of Medical Journal Editors decided to require prior recording in a protocol registry.<sup>22 23</sup>

We propose to take advantage of the work done by research ethics committees worldwide, as registers of human research protocols implicitly exist at this level, and we suggest capitalising on this. Moreover, the European EC/2001-20 guideline tends towards standardising clinical trial files and procedures across Europe.<sup>24</sup> Ethical review processes will almost certainly be standardised in the future.

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Contributors: ED coordinated the study, managed the data, did the statistical analysis, and drafted the manuscript. VL participated in the design of the study, coordinated the study, and managed the data. FC designed, submitted, and coordinated the study, interpreted data, and helped to draft the manuscript.

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Clinical Research Unit, DIM des Hospices Civils de Lyon, 162 avenue Lacassagne, 69424 Lyon cedex 03, France  
Evelyne Decullier *research fellow*

CCPPRB Lyon B - Hôpital Hotel-Dieu, place de l'Hopital, 69002 Lyon  
Véronique Lhéritier *research assistant*

French National Confederation of Research Ethics Committees - Hôpital Hotel-Dieu, 69002 Lyon  
François Chapuis *senior researcher*

Correspondence to: F Chapuis [francois.chapuis@chu-lyon.fr](mailto:francois.chapuis@chu-lyon.fr)