The attractive position of France in International Clinical Research

Summary of the 2006 survey assessed by Leem (French Pharmaceutical companies)

Abstract

In order to evaluate the attractiveness of France for conducting international clinical trials, a survey is performed every two years among pharmaceutical companies that are based in France or have affiliates in France. Initiated in 2006, the current survey was much more representative than the previous ones with 20 companies accounting for 61% of the French market. This survey included 352 international phase II and III clinical studies carried out in 2004 and 2005, 74 countries, 17,345 centres and 137,989 patients. France has participated to half of the overall number of international clinical trials. France ranked among the best European recruiters (0.19 patients/1000 inhabitants) at the second position behind Scandinavian countries, taking in account numbers of inhabitants. Protocols are now to be given the go-ahead by Ethics Committee (CCPPRB) within 60 days. With a high productivity in phase IIb and in oncology, France is still an attractive place to locate clinical research.

Introduction

At a time when speeding up development of medicinal products has become a priority for pharmaceutical companies, the sponsor of clinical trials, who is facing increasing international competition, will choose a country where time, quality and indeed costs will enable a trial to be carried out in the best possible conditions.

Competition between different subsidiaries of international companies has been made more intense by the time for adoption of the European directive that aims to harmonise clinical trial practice which has varied according to the country. Thus, in France, the required regulatory texts were not published until 28 August 2006, and this finally enabled this directive to be applied.

In this context of competition, LEEM (Les Entreprises du Médicament – French association of pharmaceutical companies) carries out a survey every two years which aims to evaluate France's performance when carrying out international clinical trials. The most recent surveys, one in 2002 and the other in 2004, have raised awareness among health professionals in France of the significance of the issues at stake in clinical research and of the need to react urgently and proactively.

Beyond raising awareness among the authorities and hospitals of the need for a joint reaction, the 2002 survey revealed the main advantages that France has to offer; the size of its market, its resources, access to patients and the prevalence of diseases[1]. An initial assessment of France's weaknesses noted speed of recruitment and quality, which were balanced by the advantages of the regulatory framework, which was favourable at the time, and was controlled by the Huriet law. The 2004 survey, which refined this initial analysis, using fuller international data, both qualitative and quantitative, clarified the position of France in relation to countries with which it was in competition, and contained an action plan based on the development of France's advantages: to maintain its advantages of simplicity and speed of administrative authorisations, and to develop competitive hospital-based clinical research by implementing a National Centre for Clinical Trials on Medicinal Products (CeNGEPS)[2].

A third survey, which was more representative than the previous two because of the participation of 20 pharmaceutical companies, was begun in 2006. This enabled the French context to be clarified, just before the implementation of the European clinical trials directive. Comparison of these results with

those of the 2004 survey enables the major international trends to be identified and the specific advantages of France in 2006 to be emphasised.

Methods

1. Participation of pharmaceutical companies

LEEM members participated voluntarily, and were subject to a rigorous process of information, training and monitoring. All LEEM members were informed of the survey. Within each French subsidiary, project managers were identified and trained in questionnaire use and methodology. The departments questioned were those responsible for managing clinical trials and operations: Clinical Development departments and/or International Medical Affairs departments in the global headquarters (or 'Corporate'), European clinical development departments and/or Medical Affairs departments and Medical Directorates and/or Clinical Development directorates of French subsidiaries.

2. Scope of surveys

The survey is limited to international phase II and III studies that are intended for registration (including extensions of indication), financed by the companies' global and/or European head offices, and involving the French subsidiary, for which the first patients were recruited between 1 January 2004 and 31 December 2005, including all methodologies and including trials sub-contracted to CROs (Contract Research Organisations) and directly monitored by the parent company or the European Region, making the distinction between trials that are sub-contracted in their entirety and those for which monitoring has been sub-contracted in at least one country.

3. Quantitative performance indicators

The three main quantitative performance indicators that have been gathered represent the level of recruitment, which can be divided into 3 variables: the number of studies, the number of patients per study and the number of patients recruited per centre, speed of recruitment which is defined using the number of patients recruited per centre and per month, and the quality of observations, which is defined by the number of 'queries' per patient recruited.

Analysis of the main indicators is subject to supplementary analysis by sub-group according to the country of origin of the pharmaceutical company, study phase and range of treatments being studied.

3.1 Data specific to France

Other performance criteria that are adapted to the French situation have been included in the French part of the study: number of protocols submitted to and accepted by CCPPRB (Ethics Committees), time elapsed before opinion is obtained from CCPPRB, dates on which the 1st and last hospital agreement are signed, and whether France is chosen to be part of international programmes.

3.2 International comparative data

To enable comparative analysis with the 2004 survey, the same groups of countries were chosen, without taking into account new members of the European Union, who only joined the Union at the end of the period in question.

4. Qualitative performance indicators

As in previous surveys, global and/or European head offices were asked to fill in a qualitative questionnaire to show their perception of the performance and attractiveness of each country to international clinical research. They were asked to give a score between 0 (minimum) and 5 (maximum) to their perception of 3 qualitative performance indicators which were designed to assess productivity in clinical research, the potential for recruitment and infrastructure and healthcare system quality.

The ‘productivity of clinical research’ was assessed as a function of cost of clinical development, the quality of investigators, speed of recruitment and adherence to recruitment aims. The ‘recruitment potential’ was judged to be the size of the market and the number and availability of patients/subjects. ‘Infrastructure and healthcare system quality’ included the importance of registration authorities, the importance of key opinion-leaders, quality of medical care in the country, clinical research organisation and how simple it is to obtain administrative authorisation.

5. Cost study

The cost study was carried out by the American firm Fast Track Systems using its database, Fast Track Systems' Trialspace Grants Manager: PICAS® industry cost benchmarking database. The data compiled in this database are provided by 110,000 investigators and around fifty pharmaceutical or biotechnology companies.

6. Data collection and analysis

6.1 Quantitative and qualitative study data

Study data were collected by the companies themselves and were sent in electronic form directly to an independent strategic consultancy, AEC Partners (Paris) which was responsible for monitoring, consolidating and analysis of data for all pharmaceutical companies. Each company was responsible for the quality and coherence of the data it provided.

Data analysis was carried out according to the following principles:

- Respect for integrity of data as sent
- Studies which did not involve France were excluded
- A company was not taken into account for an indicator if the response rate was less than 50%
- Country data were not taken into account if the number of open centres and patients recruited was zero
- For the criteria ‘percentage of centres enrolling at least one patient’ and ‘average number of patients recruited per centre’ countries with no patients recruited are taken into account but only if open centres and length of study demonstrate active international recruitment
- Country data are not taken into account if they are inconsistent: for example, if there are no recruitment centres but the number of patients recruited is greater than zero, or if the number of recruiting centres is greater than the number of open centres
- If a country does not have a figure for 'recruitment centres': patients recruited is equal to zero, with a number of recruitment centres that is greater than zero, these data are not taken in account.

- If a country does not use the 'speed of recruitment' indicator: if the number of patients recruited is zero and the length of recruitment is greater than zero (but this is taken into account for other indicators), this indicator is not taken in account.

6.2 Cost data

The cost analysis given in this publication was carried out by Fast Track Systems and is limited to data from phase II and III studies carried out in France, the United States, the United Kingdom, Italy and Poland in the period 2000-2006. All costs are given per patient and have been converted into dollars using the exchange rate published in the Wall Street Journal on 1 August 2006.

Results

Between January and May 2006, 20 pharmaceutical companies and members of LEEM, representing more than 61% of the French market (2005 data), participated in this study (Table I). 13 of these did not participate in the previous survey. Four French companies are included, which represent 22% of the French market (2005 data). Participating European (apart from France) and North American companies represent 16.7% and 22.4% of the French market, respectively (2005 data). The survey involved 352 studies, 74 countries, 17,345 centres and 137,989 patients.

1. Data specific to France

The twenty companies that took part provided data on studies carried out in France. Data for 352 studies were provided.

1.1 Time taken to begin studies

52 studies were eliminated from analysis based on ethics committee because of: lack of name of ethics committee (N=2), no key date provided (N=15), inconsistent dates (N=16) and questionnaire unable to be analysed because of lack of data (N=19). The 300 studies which were analysed were submitted to 43 ethics committees (Figure I). A quarter of ethics committees (11 CCPPRB/ethics committees) were very demanded and dealt with 146 studies, almost half the total files (49%), the median number being 4 studies per committee, with a minimum of one study and a maximum of 33 studies per committee.

The median period of time before a protocol is approved by the ethics committee is less than two months (50 days), of which 25 days represent the period of time between submission and initial response. This period seems to be shorter (49 days) for the more demanded committees (which dealt with more than 10 files) compared with median periods of 55 and 53 days respectively for the groups of committees which dealt with between 5 and 9 studies and 4 studies at most. However, this figure varies significantly, between 41 and 68 days, among the most demanded ethics committees.

The median period elapsed between submission of a file to an ethics committee and the initial signature (median period: 140 days) and the final hospital contract (median period: 299 days) varies by a factor of 2. Median period before signature of the initial hospital contract remains 90 days, after deduction of the median period between submission of a protocol and the protocol being approved by an ethics committee, but there are still significant variations between studies.

1.2 Quantitative analysis

1.2.1 Performance indicators

Quantitative analysis of studies carried out in France included 329 phase II and III studies (93.5% of studies reported), 23 studies having been excluded because of lack of data or patients recruited - these studies involved 2583 centres and 14,993 patients. The number of studies included in the scope of this survey is 2.5 times higher than in the 2004 survey (329 vs.134), and the number of patients recruited has doubled (14,993 vs. 7,141).

France's participation in international trials varies according to the pharmaceutical company's country of origin. American countries are the major contributor of studies carried out in France (151 studies, which is 46% of all studies, with 6116 patients recruited in 1050 centres), and have a market share approximately equal to that of French companies (22.4% vs. 22%), followed by European (not French) companies with 33% of studies (110 studies, 4760 patients recruited in 814 centres) and French companies with 21% of studies (68 studies, with 4117 patients recruited in 719 centres).

Studies carried out in France are for the most part phase III studies (97 phase II studies and 226 phase III studies). 2100 centres are involved in phase III studies, and 430 are involved in phase II studies. Phase III studies recruit more patients (N=11,958 or 80%) than phase II studies (N=2644 patients, or 18%).

Despite the predominance of phase III studies, phase IIb studies are proving very productive, as shown by their rapid speed of recruitment (2.1 patients/centre/month) when compared to phase III studies (phase IIIA: 1.3 patients/centre/month – phase IIIb: 1.1 patients/centre/month).

A quarter of the studies (82) were carried out in oncology/haematology, involving 2823 patients (19%), followed by cardiovascular/diabetes/obesity (22%, 73 studies) which recruited the quarter of the patients (N=3807), central nervous system/geriatrics (14.5%, 48 studies with 2841 patients), infectious diseases/virology (11%, 36 studies with 1646 patients) and inflammatory diseases/rheumatology (9.5%, 31 studies with 983 patients). The speed of recruitment was faster for cardiovascular/diabetes/obesity studies (1.6 patients/centre/month) and for those involving the central nervous system (1.5 patients/centre/month) than for other treatment areas (inflammatory diseases/rheumatology: 1.1; oncology/haematology: 1.0; Infectious diseases/virology: 0.7). The most productive areas were inflammatory diseases/rheumatology with 7.6 patients recruited per centre, and this was followed by diseases of the central nervous system (6.1 patients/centre), cardiovascular/diabetes/obesity and oncology/haematology (5.8 patients/centre) and infectious diseases/virology (4.7 patients/centre).

1.2.2 Choice of France in international programmes

14 pharmaceutical companies (70% of responses) answered the question on the choice of France for international programmes. Of the 439 studies carried out worldwide which were reported by these companies, 309 were proposed in France (70% of studies) and 217 (half of all studies) were carried out in France. The principal reason for a French subsidiary refusing participation to a study seems to have been non-feasibility of the protocol. The country of origin of the pharmaceutical company has an effect on the proportion of international studies carried out in France: French companies carry out on average 92% of their international studies in France, while European (not France) and American companies carried out 52% and 48% respectively of their international studies in France.

2. International data comparison

17 companies had access to international data which enabled France to be compared to other countries using quantitative criteria (8 American, 5 European and 4 French companies) and 12 companies were able to provide qualitative data.

2.1 Quantitative analysis

The fact that more companies participated in this survey than in the previous one enabled twice the number of international studies to be analysed (258 vs. 134) with 1.6 times as many patients recruited (137,989 vs. 86,368), with 1.4 times as many centres (17,345 vs. 12,431) and with 1.3 times as many countries involved (74 vs. 55). More than one third of studies are carried out in the field of oncology/haematology (Figure II).

The average response rate for pharmaceutical companies per study is 96%, 69% and 23%, for the number of patients per centre, speed of recruitment and quality of observations respectively.

2.1.1 Recruitment levels

France took part in all 258 studies as, by definition, only studies involving France were examined. France has 8% of all patients recruited worldwide, and is behind the United States (17%), Eastern European countries (15%) and Germany (9%) (Table II). The weight given to France, expressed in number of patients recruited, varies according to the company's country of origin (12% for French companies compared to 7%-8% for others), which confirms the existence of a 'national preference'. The weight attached to Europe is also significant, because of study selection criteria, with over 61% of all patients recruited (Table II). Within Europe, Eastern European countries are the heaviest recruiters, with 25% of all patients recruited, followed by Germany (15%), France (14%), Scandinavia (14%) and other Western European countries (14%).

Analysis taking into account the populations of the different countries enabled a ratio to be defined for each country, expressing the number of patients recruited per 1000 inhabitants (Table III). France, with a ratio that is above the European average, is in second place behind Scandinavia.

This survey reveals a reduction in the number of patients recruited per study for all countries (53 vs. 71 in 2004) and for European countries (46 vs. 53 in 2004) and that this figure remained stable in France (46 patients per study) which is certainly behind its major international competitors but which remains around the European average, close to Italy, Spain and the United Kingdom (Table II). All countries have also experienced a decline in the number of patients recruited per centre (Table II).

Analysis by study phase (98% of responses) shows that the number of patients recruited per centre, considering all countries, is higher in phase III (IIIa: 8.3 and IIIb: 7.4 patients/centre) than in phase II (IIb: 7.2 and IIa: 6.6). France recruits more patients in phase IIb studies (7.2 patients/centre) than in phase III studies (phase IIIa: 6.7 – phase IIIb: 5.8), which is around the average for European countries, with Eastern European countries ahead (10.6 patients/centre). Asia is the geographical area which recruits the highest number of patients for phase III studies (12.1 patients in phase IIIa and 11.6 in phase IIIb).

Breakdown by treatment areas shows an average number of patients recruited per active centre, considering all countries combined, of 10.3 for cardiovascular/diabetes, obesity, 9.2 for inflammatory diseases/rheumatology, 7.5 for the central nervous system, 6.2 for oncology/haematology and 6.1 for virology/infectious diseases. With 6.1 patients recruited per centre, France occupies an important position in the field of oncology. Within oncology alone (70 studies), analysis shows that France lies around the European average for attractiveness in phase II, with a number of patients in phase IIa (89 patients) which places it behind Scandinavia (108 patients) and a number of patients in phase IIb (549 patients) which places it in the leading group, behind the United States (866 patients) and Eastern European countries (644 patients).

2.1.2 Speed of recruitment

The response rate for the speed of recruitment criterion was 69%, or 15 companies, with 95,422 patients involved. The average speed of recruitment was 1.7 patients per centre per month, on a European level and when all countries are combined (Figure III). The Eastern countries remain the strongest, with a speed of 2.5 patients recruited per centre per month. The United States, the United Kingdom and Canada seem to be the worst performing countries, with speed of around 1. France sets itself apart from its major competitor countries, with a stable speed of recruitment of 1.4 patients recruited per centre per month (compared to 1.5 patients/centre/month in 2004), which is 7% higher than the speed in Germany, 29% higher than the speed in the United Kingdom and 43% higher than the speed in the United States. However, the speed in France is 1.8 times lower than that of Eastern European countries.

Furthermore, France is still well within the average range for major Western countries for all phases and confirms its high level of productivity in phase IIb, with a higher recruitment rate (phase IIb: 2.2 – phase IIa: 1.6 – phase IIIa: 1.2 and phase IIIb: 1.1 patients/centre/month).

Analysis by treatment area shows an average speed of recruitment for all countries combined of 2.4 patients/centre/month for the areas of inflammatory diseases and rheumatology, which is close to the speed in cardiovascular/diabetes/obesity (2.3 patients/centre/month), to 1.6 patients/centre/month for the central nervous system, and 0.9 patients/centre/month for the fields of oncology/haematology and virology/infectious diseases. France's good performance in the quantitative criterion in oncology/haematology (1 patient/centre/month) and central nervous system (1.7 patients/centre/month) should be emphasised. Just in oncology (70 studies), France is in 2nd place in terms of speed of recruitment (for phase IIb studies (1.5 patients/centre/month), behind the Eastern European countries (2.9 patients/centre/month).

2.1.3 Quality of observations

The low response rate for this criterion (21%, or 9 companies, 30,254 patients), combined with a higher proportion of responses which concerned only France, means that these results should be analysed with prudence (Figure III).

Two points should be emphasised: firstly, the low proportion of studies that were sub-contracted, and second, the importance of the availability of electronic case report forms. 42 studies (17.4%), out of the 242 studies for which information on the sub-contracting criterion was provided, used this service. Because of the small numbers, these data do not enable the type of sub-contracting (partial or total) to be evaluated. Information on the electronic case report forms criterion was provided by all companies apart from one (97% of responses). 41 studies (16%) of the 251 studies for which information was provided benefited from electronic case report forms. Use of such a report form seems to have a significant impact on all productivity criteria, as illustrated in Figure IV.

2.2 Qualitative analysis

12 companies answered the qualitative questionnaire. These companies were French, European (not France) and American, with market share in France (2005 data) of respectively 19.8%, 4.4% and 14.2%, which means that French companies were heavily weighted. Table IV shows the results (scores from 0 to 5) of qualitative performance indicators for the following five major countries or geographical areas: Germany, Eastern Europe, France, United Kingdom and the United States.

The significance of France as a key European market is confirmed in this new survey (average score is stable at 3.7) both in economic terms and in terms of patient availability. The quality of infrastructure and the healthcare system in France is appreciated (average score of 3.6), and medical treatment in France is still perceived as being excellent (score of 4.2). On the other hand, France suffers from a perception that its administrative procedures for authorisation are not simple, while it obtained the best score in 2004 (2.8 vs. 3.4), and the United States takes first place. Pharmaceutical companies' opinions on productivity of clinical research in France remains the same as in 2004 (a score of 2.8), which still bears the impact of the slowness and lack of respect for recruitment aims, despite the fact that investigators are perceived to be of high quality and that French development costs are perceived to be in line with the European average.

3. Cost data

Analysis of reported costs per patient shows that France remains an attractive country in this respect. In 2005, cost per patient in France was evaluated at $3532, which is lower than costs in Poland and the United Kingdom, where per-patient costs are over $5500, Germany ($6800), Italy ($9600) and the United States ($13,000) where per-patient costs are highest. Over the last 5 years, these costs have been relatively stable in Germany, Poland and France (apart from two steep rises in 2001 and 2004), and have decreased in the United Kingdom (2000 figures: $7600), and have increased by around 40% in the United States (2000: $9200) and have almost doubled in Italy (2000: 5100 $).

Discussion

This 2006 survey is more representative than the 2004 survey, as more companies took part (20 this time, as against 10 in 2004) and a better balance of companies (calculated using turnover) by country of origin (France: 22% vs. 20.6, Europe outside France: 16.7% vs. 5.1%, United States: 22.4% vs. 10.8%.

However, as in the previous study, international studies were chosen because of the fact that there was a French involvement, which meant that there was a methodological bias in France's favour, which was deliberately done in order better to understand the French experience in this field and to define the current state of art of clinical research in France. A major advantage of this survey is the fact that France's participation in international programmes was examined for the first time. As for comparisons between countries, as the scope of various countries' participation varies between studies, analysis of these results only enables trends to be identified.

Due to the significance of the survey carried out on studies done in France (352 studies, 17,345 centres, 137,989 patients), results on periods of time taken for ethics committees to approve studies and signature of hospital contracts may be considered to be representative of studies promoted by the pharmaceutical industry and carried out in 2004-2005. Periods of time taken by AFSSAPS (French Agency for the Safety of Healthcare Products) to respond were not collected as, during this period, the Huriet law still applied, and there was a simple declaration regime. A pilot phase in compliance with the directive was implemented at the end of 2004/beginning of 2005 but this was optional and was reserved, for half this period, for phase I studies.

This survey confirms the findings of the IGAS (General Inspection for Social Affairs) report, which showed that not all ethics committees are demanded (43/48) and that work is not evenly spread – a quarter of all committees respond to half of all requests. The committees that deal with the greatest number of files are also the fastest. However, it should be emphasised that, in the context of the Huriet law, which laid down a 5-week period for responding, from the date on which the complete file is received, with a 30-day extension if supplementary information is requested, ethics committees were providing an initial response within, on average, 25 days, and an opinion in 50 days.

These periods conform to those required by the directive. It is important that this is maintained when the new style Ethics Committees are established). Ethics committees (CPP - French ethics committee) have a broader structure with 2 colleges (one scientific, the other community-based) and include statutory patients' and healthcare users' organisations. Furthermore, quorums are now required, and 7 members (of 14) must be present, of which 3 members must belong to the scientific side (and one must be competent in biostatistics or epidemiology) and 3 other members from the community side (and one must be from the patients' and healthcare users' associations). Ethics committees are being given new responsibilities. In addition to biomedical research and the substantial changes being made to it, the tasks of ethics committees have been widened in scope, particularly in terms of studies of current treatment and of biological sample collections.

Turning to hospitals, the fact that establishing studies is a slow process, which is in part linked to administrative constraints (signature of contracts), had been emphasised in previous surveys.

The alarming figures revealed in this survey show that time taken for hospital administration is today a major constraint when initiating a study (140 days before the initial hospital contract is signed). If pharmaceutical companies are awaiting a favourable opinion from an ethics committee in order to submit a request for a hospital contract, the period before this contract is signed remains 90 days. An aim for the future, which is wished for by the pharmaceutical industry, is that submissions are made to an ethics committee and a hospital contract requested in parallel, and that the period between submission and signature of a hospital contract be reduced to a maximum of 60 days. Establishment of CeNGEPS should enable the period that elapses between submission and signature of a hospital contract to be shortened.

Analysis of studies carried out in France also enables us to emphasise that France performs well in early stage studies, which is a major factor in France's attractiveness, both in terms of the number of patients (N=2644) and the number of active centres (N=430) and speed of recruitment (phase IIa: 1.3 – phase IIb: 2.1 patients/centre/month). Thus, thanks to high levels of technical expertise, France must be recognised internationally for its proof-of-concept studies and must also become one of the most important centres of translational research. This is developing particularly quickly in

oncology/haematology, which has been an area in which France was already excelling in 2004, and this continues in 2006. Establishment of cancer centres organization ('cancéropoles') and development of hubs of competitiveness should enable further strengthening of French clinical research in the early stages of development.

Moreover, for the first time this survey enabled the importance of feasibility studies to be emphasised. These are essential for a French subsidiary in order to enable an international study to be carried out in France. However, this demands high levels of responsiveness on the part of the subsidiaries, and it is sometimes impossible to anticipate demand, and response periods are non-negotiable constraints. Moreover, the possibility of refusing participation to a study must be retained, thus avoiding involvement in a study for which recruitment is impossible. Implementation of CeNGEPS should thus enable these surveys to be carried out more effectively, and in particular will provide a map of centres of expertise broken down by treatment area.

Today, such feasibility studies are even more difficult for an American company to carry out (48% of studies carried out in France) or European (not France) (52% of studies carried out in France) than for a French pharmaceutical company (92% of studies carried out in France). Work must be done to improve acceptability of some protocols from English-speaking countries by French teams, for example by, in advance, making the protocol writing process easier in collaboration with manager from the countries in which the study is proposed.

Likewise, in order to improve hospital productivity, accessibility to electronic case report forms must be improved.

Compared to the 2004 survey, the position of France in terms of the quantitative criteria seems stable in comparison to other countries. Anxieties raised by the 2005 AFSSAPS[4] figures (1098 studies in 2003, 1223 studies in 2004 and 1045 studies in 2005) show that although there were, in absolute terms, fewer studies carried out in France in 2005, this reduction was also observed in other European countries, for example in Germany (1393 studies in 2003, 1735 studies in 2004 and 1225 studies in 2005). This reduction was balanced by a higher number of studies in 2004, which was due to fear caused by

implementation of the directive, and pharmaceutical companies may well have prioritised studies in 2004 before this occurred.

Quantitative analysis, just like qualitative analysis, generally reveals the same strengths and weaknesses as in 2004. Despite a methodological bias in its favour, France only has 8% of patients recruited worldwide, which is less than half the number recruited in Eastern Europe, while France is still seen as one of the most attractive countries in terms of recruitment potential. However, when the demographic component is taken into account, it is revealed that France makes a strong worldwide contribution to patient recruitment and that this contribution has continued to increase over the past two years (ratio of patients/1000 inhabitants: France: 0.19 vs. 0.12 in 2004 – Germany: 0.16 vs. 0.12 in 2004 – Italy: 0.1 vs. 0.05 in 2004, Eastern Europe: 0.07 vs. 0.04, and United Kingdom: 0.08 vs. 0.07).

This survey confirms that there is a significant mismatch of perception between quality of French medicine and infrastructure and the productivity of clinical research in France, which is demonstrated by a lower recruitment rate, despite the attractive costs of clinical development. However, the low cost per patient needs to be seen against higher monitoring costs which arise because of the slow recruitment process.

It is nonetheless interesting to note that in terms of perception of administrative simplicity, France scored worse. This is certainly linked to the European directive, and again to its delayed implementation in France.

It should also be noted, in analysis of competition, that not all European countries have shown the same trends, either in terms of the quantitative or qualitative criteria. Differences are appearing between Eastern European countries, with the emergence of countries such as Croatia and Bulgaria, while other countries, such as Hungary and Poland, now have profiles that are increasingly similar to those of Western European countries. While France, Germany and Eastern European countries have remained stable, Italy and Scandinavia have made progress, and the United Kingdom has fallen behind. Asian countries would appear to have a fairly attractive potential for development.

This international comparison shows that France has, over the past two years, shown good resistance to changes linked with implementation of the directive. France still has a significant number of potential

patients, and one of its major advantages in terms of attractiveness concerns the early phase IIa-IIb stages, proof of concept, particularly in the areas of excellence (cardiovascular/metabolic, neurodegenerative, haematology/oncology and infectious diseases) in which it must continue to invest. Such investment must be accompanied by convincing communications, as France's image does not match the reality, as confirmed by the analysis of perception when compared to the actual situation.

Conclusion

These survey results are significant because of the number of companies participating, which represent more than 60% of the French market. French pharmaceutical companies are adopting policies whereby they make significant investments into Clinical Research in France, as are American companies, which are participating in the survey for the first time. This survey shows that France takes part in half of international programmes initiated by parent companies.

Over two years, France and Germany have maintained their respective positions within international Clinical Research. Other European countries such as Italy, Spain and Scandinavian countries have made progress, while others such as the United Kingdom have fallen back. The position of Eastern European countries has remained stable. Expected breakthroughs from Latin America and Asia have not yet occurred.

Implementation of CeNGEPS will enable optimisation of organisation of Clinical Research in France, which will have a positive impact on productivity and quality of results. Establishment of cancer centres (‘cancéropoles’) and development of hubs of competitiveness are real assets that will strengthen French clinical research, in particular the early stages.

Today, the fact that the 60 day period for ethics committee approval of a protocol is respected, the expertise of French medical teams in fields such as oncology and cardiovascular medicine, and the quality of France’s infrastructure and medical care all help to make France an attractive country for international Clinical Research.

Abbreviations

AFSSAPS: French Agency for the Safety of Healthcare Products

CCPPRB: Consultative Committee for the Protection of Persons involved in Biomedical Research (Ethics Committees)

CeNGEPS: National Centre for Management of Clinical Trials of Healthcare Products

CCP: Committee for Protection of Persons (Ethics Committee)

CRO: Contract Research Organization

IGAS: General Inspectorate for Social Affairs.

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Table I :

Share of French market of 20 companies participating in the survey, according to country of origin

Country of origin	Participating companies	Share of French market in 2006 survey (2004 survey)
FRANCE	**Sanofi-Aventis, Servier, Pierre Fabre, Ipsen**	**22% (20.6%)**
EUROPE (not France)	**AstraZeneca, Novartis, Roche, Bayer, Schering, Boehringer Ingelheim, Altana Pharma**	**16.7% (5.1%)**
UNITED STATES	**Pfizer, BMS, MSD, Janssen Cilag, Wyeth, Lilly, Abbott, Gilead, Idenix,**	**22.4% (10.8%)**

(Source: GERS - 2005 data)

Table II :
Comparative levels of recruitment by country or geographical area as shown in the 2006 and 2004 surveys (France participated in all studies)

		Studies (n)	Patients recruited [n(%)]	Patients/study (n)	Patients/active centre (n)
France[a]	2006	258	11,637 (8%)	46	6.3
	2004	*134*	*7147 (8.3%)*	*52*	*7.6*
Other Western Europe[b]	2006	186	11,642 (8%)	30	7.4
	2004	*77*	*6388 (7.4%)*	*38*	*7.2*
Germany	2006	169	12,725 (9%)	66	6.8
	2004	*93*	*7602 (8.8%)*	*73*	*7.3*
Scandinavia/Northern Europe[c]	2006	145	10,479 (8%)	33	7.4
	2004	*59*	*3738 (4.3%)*	*37*	*9.4*
Spain	2006	135	6,377 (5%)	47	6.5
	2004	*82*	*3672 (4.3%)*	*45*	*6*
Eastern Europe[d]	2006	127	21,108 (15%)	65	10.4
	2004	*68*	*12,277 (14.2%)*	*85*	*15.8*
Italy	2006	120	5,755 (4%)	48	6.6
	2004	*72*	*2991(3.5%)*	*42*	*7.2*
United Kingdom	2006	103	4,609 (3%)	45	5.6
	2004	*83*	*3916 (4.5%)*	*47*	*7.2*
EUROPE[e]	2006	**258**	**84,332 (61%)**	**46**	**7.5**
	2004	***134***	***47,731 (55.3%)***	***53***	***8.8***
United States	2006	138	23,132 (17%)	168	6.1
	2004	*75*	*15,476 (17.9%)*	*206*	*5.9*
Canada	2006	126	6,517 (5%)	47	6.2
	2004	*69*	*5842 (6.8%)*	*85*	*5.8*
Australasia/South Africa[f]	2006	122	8,062 (6%)	49	8.3
	2004	*68*	*4926 (5.7%)*	*55*	*8.0*
Latin America[g]	2006	93	7,944 (6%)	38	9.1
	2004	*18*	*8379 (9.7%)*	*190*	*25.1*
Asia[h]	2006	50	4,997 (4%)	58	11
	2004	*11*	*3029 (3.5%)*	*108*	*20.3*
Middle East[i]	2006	47	3,005 (2%)	55	8.9
	2004	*16*	*985 (1.1%)*	*49*	*18,.7*
All countries	2006	**258**	**137,989 (100%)**	**53**	**7.7**
	2004	***134***	***86,368 (100%)***	***71***	***9.4***

Table II : (continued)

a The total number of 258 studies in 2006 and 134 in 2004 also represent all studies carried out in France and in Europe
b Andorra, Austria, Belgium, Cyprus, Greece, Ireland, Malta, Netherlands, Portugal and Switzerland
c Scandinavia, Denmark, Finland, Iceland, Norway and Sweden
d Bulgaria, Croatia, Estonia, Hungary, Latvia, Lithuania, Poland, the Czech Republic, Romania, Russia, Slovakia, Slovenia, Ukraine
e All countries on the continent, particularly Western and Eastern Europe and Scandinavia
f South Africa, Australia and New Zealand
g Argentina, Brazil, Mexico, Chile, Colombia, Peru, Puerto Rico, Guatemala, Costa Rica and Venezuela
h China, South Korea, Hong Kong, India, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan and Thailand
i Saudi Arabia, Egypt, Israel, Lebanon, Tunisia and Turkey

Table III : Number of patients as a proportion of the population

	Population* (millions)	Number of patients/1000 inhabitants	
		2006	***2004***
France[a]	61	0.19	*0.12*
Other Western Europe[b]	61	0.19	*0.10*
Germany	82	0.16	*0.09*
Scandinavia/Northern Europe[c]	25	0.42	*0.15*
Spain	43	0.15	*0.09*
Eastern Europe[d]	295	0.07	*0.04*
Italy	58	0.10	*0.05*
United Kingdom	59	0.08	*0.07*
EUROPE[e]	**684**	**0.12**	***0.07***
United States	298	0.08	*0.05*
Canada	32	0.20	*0.18*
Australasia/South Africa[f]	68	0.12	*0.07*
Latin America[g]	468	0.02	*0.02*
Asia[h]	3038	0.00	*0.00*
Middle East[i]	188	0.02	*0.01*
All countries	**4776**	**0.03**	***0.02***

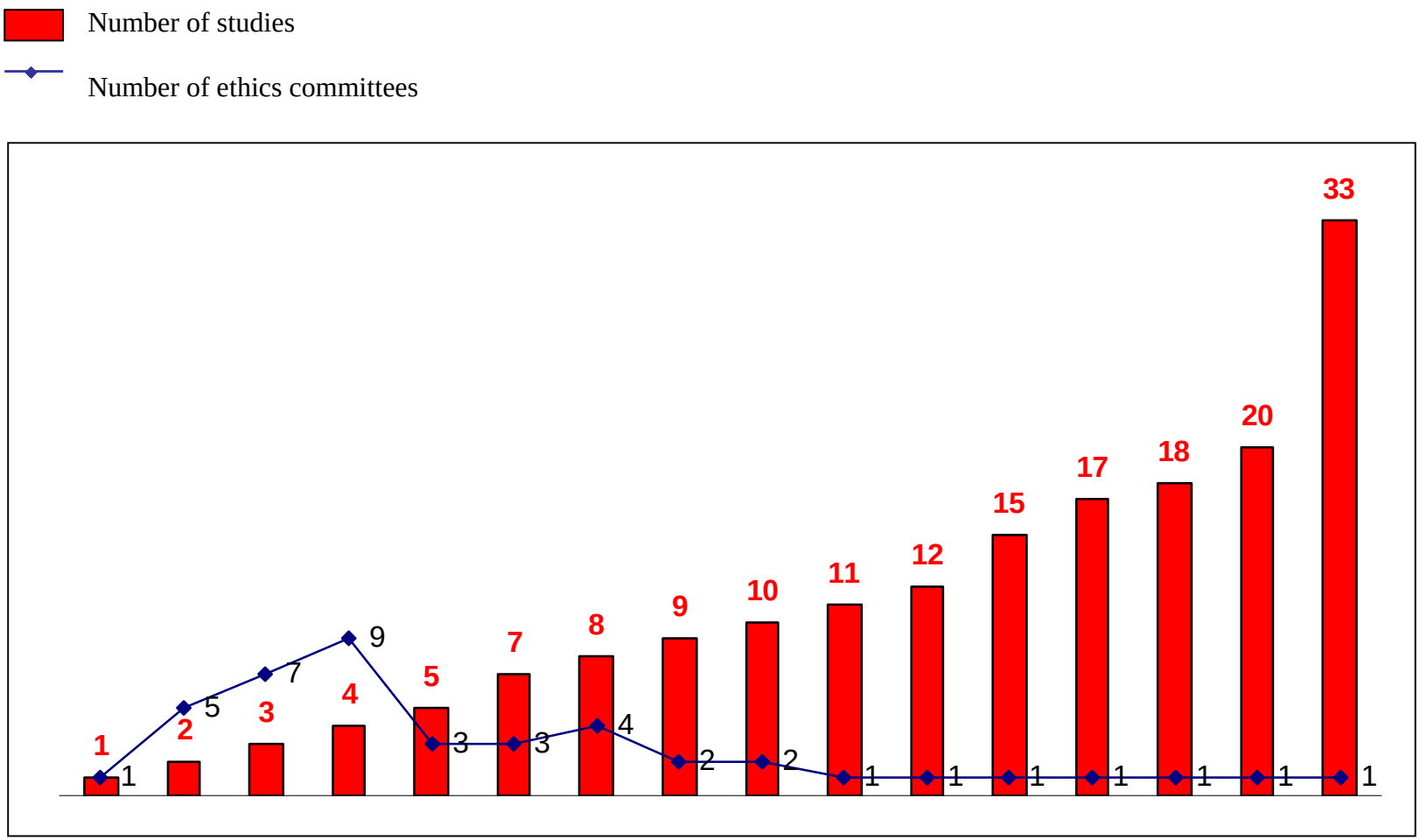
* Source: populationdata.net 2006
a The total number of 258 studies in 2006 and 134 in 2004 also represent all studies carried out in France and in Europe
b Andorra, Austria, Belgium, Cyprus, Greece, Ireland, Malta, Netherlands, Portugal and Switzerland
c Scandinavia, Denmark, Finland, Iceland, Norway and Sweden
d Bulgaria, Croatia, Estonia, Hungary, Latvia, Lithuania, Poland, the Czech Republic, Romania, Russia, Slovakia, Slovenia, Ukraine
e All countries on the continent, particularly Western and Eastern Europe and Scandinavia
f South Africa, Australia and New Zealand
g Argentina, Brazil, Mexico, Chile, Colombia, Peru, Puerto Rico, Guatemala, Costa Rica and Venezuela
h China, South Korea, Hong Kong, India, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan and Thailand
i Saudi Arabia, Egypt, Israel, Lebanon, Tunisia and Turkey

Table IV : Qualitative indicators by country or geographical area (expressed as a mean score[a])

	France	Germany	United Kingdom	Eastern Europe[b]	United States
Potential for recruitment	**3.7**	**3.5**	**3.5**	**3.8**	**3.7**
Availability of patients	3.3	3.3	3.3	3.8	3.8
Size of market	4.1	3.3	3.3	3.8	3.1
Infrastructure quality	**3.6**	**3.6**	**3.4**	**2.4**	**3.8**
Importance of opinion-formers	4.2	4.0	4.0	2.2	4.2
Simplicity of administrative authorisation process	2.8	3.3	2.5	2.5	3.4
Importance of registration authorities	3.9	3.5	3.8	2.0	4.1
Quality of medical treatment	4.2	4.0	3.3	2.4	3.8
Clinical research organisation levels	2.9	3.3	3.3	2.9	3.7
Productiveness of clinical research	**2.8**	**3.1**	**2.6**	**3.7**	**2.5**
Attractiveness of development costs	2.7	2.4	2.2	3.7	1.8
Quality of investigators	3.3	3.5	3.2	3.4	3.1
Recruitment rate	2.7	3.1	2.4	3.8	2.4
Consistency with recruitment aims	2.7	3.3	2.6	3.8	2.8

a score calculated for each criterion, from 0 (least good) to 5 (best)
b Bulgaria, Croatia, Estonia, Hungary, Latvia, Lithuania, Poland, the Czech Republic, Romania, Russia, Slovakia, Slovenia, Ukraine and Yugoslavia

Figure I : How the 300 studies are distributed between 43 ethics committees (CCPPRB)



9 ethics committees have reviewed 45 % of studies (136 studies)

Figure II : Distribution of studies by therapeutic area and by country (expressed as a % of all studies)

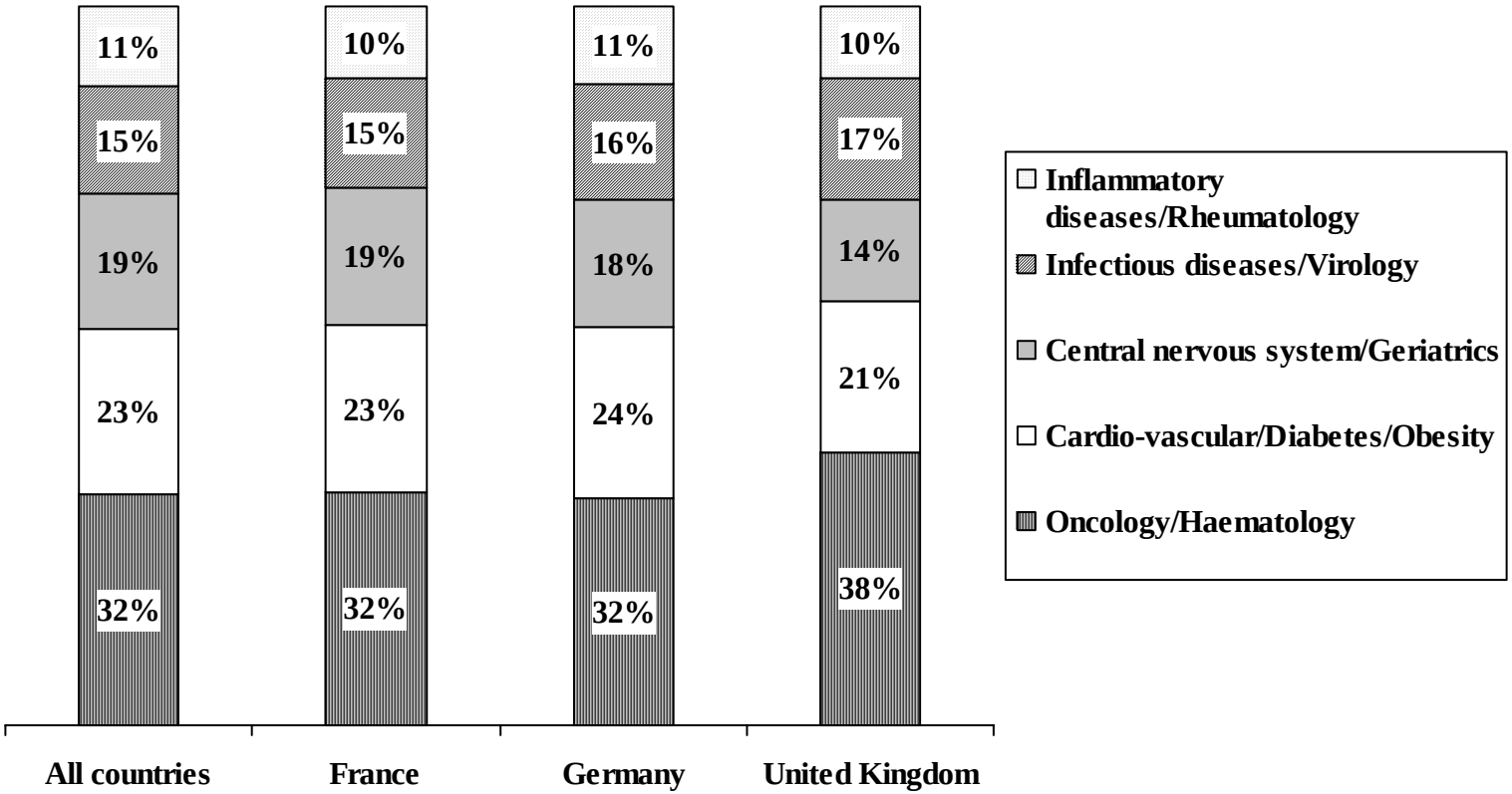
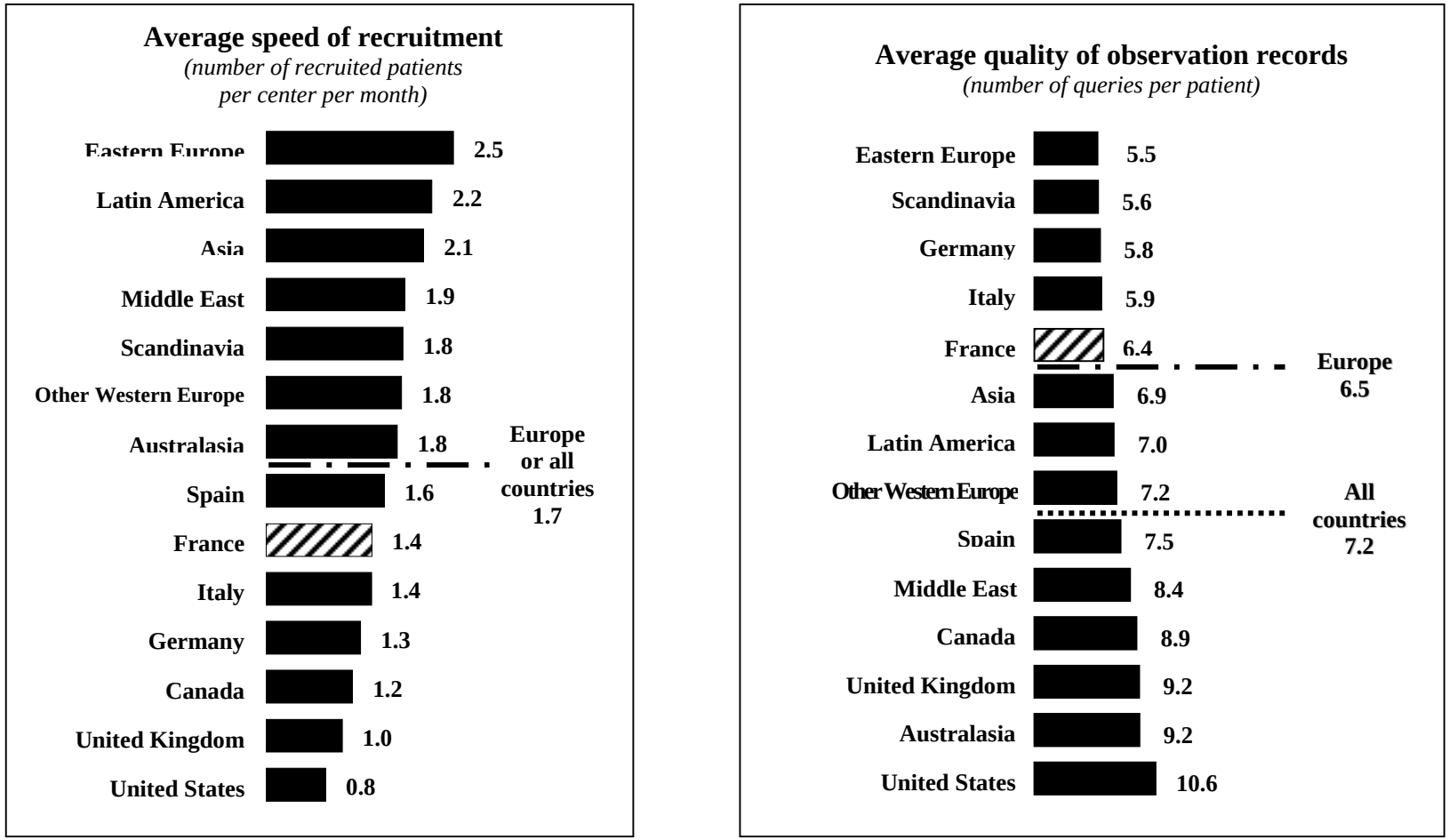
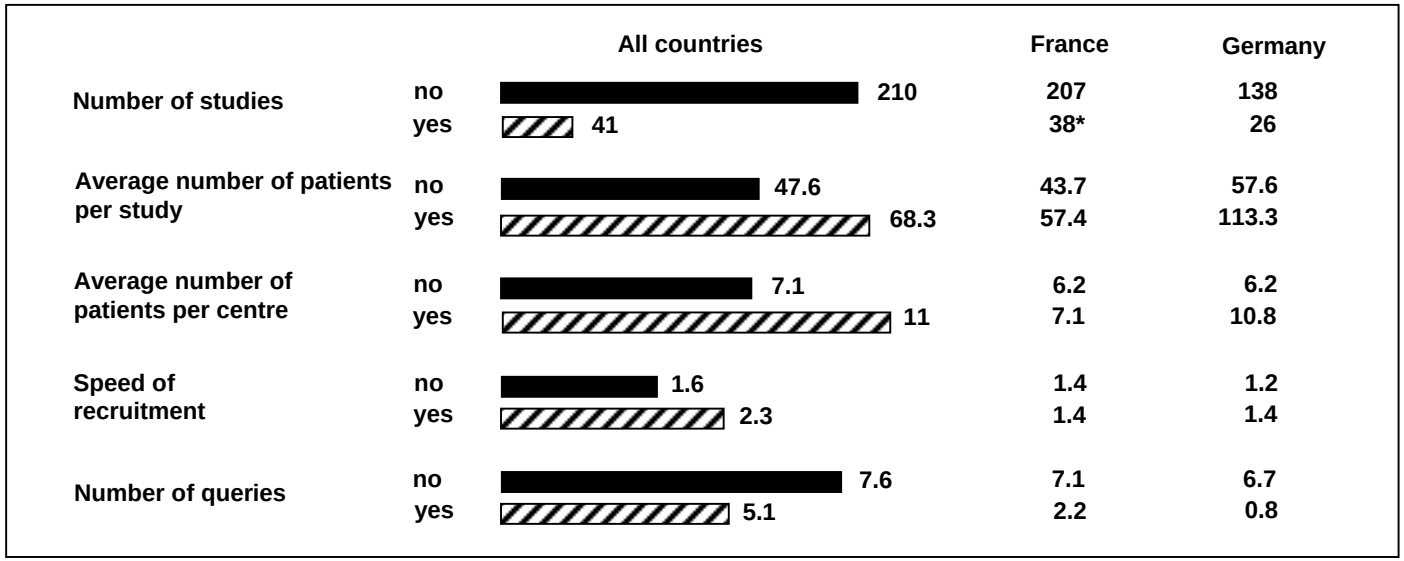


Figure III : Other quantitative performance indicators, average speed of recruitment and average quality of observation records



- Latin America : Argentina, Brazil, Mexico, Chile, Colombia, Peru, Puerto Rico, Guatemala, Costa Rica, Venezuela
- Asia : China, South Korea, Hong Kong, India, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, Thailand
- Australasia : South Africa, Australia and New Zealand
- Middle East : Saudi Arabia, Egypt, Israel, Lebanon, Tunisia, Turkey
- Eastern Europe : Bulgaria, Croatia, Estonia, Hungary, Latvia, Lithuania, Poland, the Czech Republic, Romania, Russia, Slovakia, Slovenia, Ukraine
- Other Western Europe : Andorra, Austria, Belgium, Cyprus, Greece, Ireland, Malta, Netherlands, Portugal and Switzerland
- Scandinavia : Denmark, Finland, Iceland, Norway and Sweden
- Europe : All countries on the continent, particularly Western and Eastern Europe and Scandinavia

Figure IV : Impact of use of electronic records on productivity criteria – (response rate: 97%)



Yes: if electronic records were used in the study

No: if no electronic records were used in the study

* in 3 studies, French data were not useable, probably because of problems with data entry for some information