

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors Influencing Clinical Trial Site Selection in Europe: The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study TM)
AUTHORS	Ambrosio, Giuseppe; Gehring, Marta; Taylor, Rod; Mellody, Marie; Casteels, Brigitte; Piazzini, Angela; Gensini, Gian Franco

VERSION 1 - REVIEW

REVIEWER	Henk Jan Out, MD PhD, professor of pharmaceutical medicine Radboud University Nijmegen Medical Centre, The Netherlands VP Global R&D Women's Health, Teva Pharmaceuticals
REVIEW RETURNED	24-Apr-2013

GENERAL COMMENTS	Interesting paper, although methodology used has its limitations (web survey), the conclusions are nevertheless clear and important in view of current discussion of critical variables to perform clinical trials in Europe
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REVIEWER	Dr Trudie Lang, Director, The Global Health Network Research Fellow, Green Templeton College Center for Tropical Medicine, Nuffield Department of Medicine University of Oxford I have no competing interests to declare
REVIEW RETURNED	04-Jun-2013

THE STUDY	The claims in the conclusion / discussion seem to be distant and quite a leap from the results.
RESULTS & CONCLUSIONS	<p>I fully agree with the authors that the question and subject area is very important. There certainly is not enough evidence and research in this area of clinical research operations, and the study team should be congratulated for tackling this area of exploring the factors that impact clinical trial site selection.</p> <p>However, unfortunately, I think the study itself fell somewhat short of being able to strongly support the statements made in the discussions, and this was a shame, but I think this could be addressed?</p> <p>The study was limited to an online survey and the discussion were full of strong statements that were quite difficult to relate to the findings of the survey. Perhaps this work could have been</p>

	strengthened by conducting some focus group discussions or in-depth interviews to confirm and explore more deeply the indications that were apparent from the online survey.
GENERAL COMMENTS	Well done for tackling this issue - I do think it would be worth putting in some extra effort to add to the data from the online surveys if you are able?

REVIEWER	Demotes Mainard, Jacques INSERM
REVIEW RETURNED	18-Jun-2013

GENERAL COMMENTS	<p>The objective of the article "Factors Influencing Clinical Trial Site Selection in Europe: the SAT-EU StudyTM" is to identify the weight of different factors impacting European clinical trial site selection in various decrease areas for clinical trial in Europe since 2007.</p> <p>It shows that, for industry sponsored clinical studies, the main factors for selecting the European sites are investigator, networks, hospital and environment factors. Cost aspects seem to have less importance than expected. These data are of substantial interest for policymakers in Europe and help focus on the right parameters to improve the competitiveness of Europe in clinical research.</p> <p>However some points need clarification:</p> <p>Major points:</p> <p>Contrary to what is written in the article in the introduction (Line 58, page 5: « We also investigated whether trial selection needs differ between academic and commercial sponsors".), it is clearly stated in the questionnaire that the survey is focused on industry-sponsored clinical research and indeed is not covering academic-sponsored studies.</p> <p>Thus it should also be highlighted in the article that this survey and its results concerns only industry trials. Furthermore, it also impacts on the limitations of the survey. Academic sponsors could have different priorities (particularly in terms of costs vs. timelines) and correspond to a significant number of Clinical Trials in Europe.</p> <p>- Results: It seems there are some discrepancies in responders: 20% are CTUs but the total of responders from CTU (i.e., Head of CTU or staff members from CTU in Fig. 3) corresponds to 33.8%. Please clarify.</p> <p>In the text it is said that investigator- and hospital-dependent levers combined for early phase studies have a weight of 60/100, while it seems lower on the figure.</p> <p>- Discussion: The different parts on the cost aspects in the overall article are ambiguous and too much insistent. Among the four levers it is shown to be the less important. But the results and the discussion focus on the government financial/tax incentives when cost of running trial is not discussed. After having insisted that the costs are less important than the other factors, it is highlighted that the hidden costs should be reduced. Furthermore those hidden costs are indirect and could be considered as subjective, as an author interpretation rather than based on a specific question to the stakeholders.</p>
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	<p>Some interpretations, in addition to the previous one, are too affirmative compared to the actual results:</p> <ul style="list-style-type: none"> - Discussion: On page 13: “Our survey clearly indicates that stakeholders would like a single “trial market”. The sentence is too affirmative, the question is not clearly asked in the survey and thus rather reflects an interpretation by the authors. - Conclusion: “it requires harmonised national adoption” + “aligned hospital contracting” is not supported by the results. <p>Minor points:</p> <ul style="list-style-type: none"> - Introduction: The objective is to assess the weight of different factors on the European clinical trial sites selection. The article starts with the observation of the decrease in clinical trials in Europe between 2007 and 2011 and what could have been the reason for such decrease, without hard evidence on the actual weight of those factors. But if the identification of the weight allows to improve the current situation, it won't directly explain and confirm, or not, the reasons for the decrease in the number of clinical trials in Europe. Maybe the sentence linked to the decrease in Europe should be reformulated to avoid the misunderstanding. - Methods: Survey design: How did you proceed for identifying the main criteria expected to impact site selection? <ul style="list-style-type: none"> - “The defined criteria underwent review and discussion with a small number of knowledgeable professionals”. What is this small number and most importantly how do you define “knowledgeable” professionals (what kind of position or experience...)? - Remark: Rationale for having twice the costs in aspects, this could add a bias on the impact of this factor. <p>Methods:</p> <p>It is not mentioned in the text how Biotech/Other/Medical Devices responses have been used as only CTU/CRO and Industry are described. Those 3 categories represent around 20% of the responders. Not clear in “responders demographic paragraph” (but distribution given in the figures).</p> <ul style="list-style-type: none"> - Results: 72% of question answered, ie ? 485 responders (100%) concerns the identity, but N=341/342 for the different factors and N= 253/296 for the others questions, I am not sure to understand the distribution of the questions answered per person. - Results: The results on the desirability of running trials in the EU countries are, as described, a personal perception from the responders. It would be of interest to compare it to the number of studies performed in those countries (particularly with objective data), and if some discrepancies appear they should then be discussed. - Results: The comparison of the importance of the different factors is regularly qualitative rather than quantitative. Mainly cost factor are often considered as significantly less important but the percentage of this factor is never given in the text (only to be estimated from the figure). It seems from the figure 4 that the costs factor is less important in the early stage compared to the late stage. Is this difference significant or not?
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	<p>Results:</p> <ul style="list-style-type: none"> - I am not sure to understand the interest to pool investigator- and hospital- dependents levers. - In the description of the impact of two factors is missing (Presence of country on core country list and Hospital approval/contracting system) when the other 16 appear. - Investigator driven criteria is always shown before the environment ones, except in the description in the results page 10. It would be better for the reader to keep the same order for the readers. - Discussion: By having the weight of the different factors it helps to improve the drawing power of the European sites. But it would be relevant to discuss the competitiveness with other countries. - Limitations: Probably less impact but one part of the questionnaire concerns more specifically Italy and Cardiology. Could this be a bias, meaning that maybe the stakeholders involved in cardiology studies were more willing to respond to the survey? - The result of the question (in the survey) on the rating of the countries depending on the availability of equipment doesn't appear in the article. Is there any reason? - Figure 8: lower panel: N=253 as well as the previous panel? - Ref 12: should refer directly to the EU press release rather than to the EFPIA site which refers to it for the decrease in the number of clinical trials in Europe between 2007 and 2011. <p>In summary: acceptable pending on appropriate modifications</p>
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VERSION 1 – AUTHOR RESPONSE

II. Response to reviewer Henk Jan Out, MD PhD

- Interesting paper, although methodology used has its limitations (web survey), the conclusions are nevertheless clear and important in view of current discussion of critical variables to perform clinical trials in Europe

We thank the reviewer for his praise to our work

III. Response to reviewer Dr. Trudie Lang

- I fully agree with the authors that the question and subject area is very important. There certainly is not enough evidence and research in this area of clinical research operations, and the study team should be congratulated for tackling this area of exploring the factors that impact clinical trial site selection.

We wish to thank the reviewer for her praise to our work, and for the opportunity to improve its presentation.

We answer the various comments below.

- I think the study itself fell somewhat short of being able to strongly support the statements made in the discussions, and this was a shame, but I think this could be addressed?

The study was limited to an online survey and the discussions were full of strong statements that were quite difficult to relate to the findings of the survey. Perhaps this work could have been strengthened by conducting some focus group discussions or in-depth interviews to confirm and explore more deeply the indications that were apparent from the online survey

We thank the reviewer for her advice in this respect. We obviously concur with the importance of backing statements with hard data. In fact, we do have some additional information potentially relevant to this issue, which was not presented initially due to our inability to properly convey the information, as well as due to space constraints. We have now better described the survey procedure (page 7 of the revised manuscript lines 30-45), and have toned down our statements in various places (in the Abstract of revised manuscript page 14, lines 14-55 and in the Conclusions on page 17 line 34-52). Furthermore, we now wish to provide additional material (see below) as "on line supplement".

Here, we wish to clarify some issues:

1. As a source of information within the survey, in addition to the specific responses to the question-and-answer questionnaire, we also left space for participants to provide "free text" responses if they wished so. We actually received articulated comments from most respondents: 56 comments about levers impacting trial site choice in clinical operations, and a further 253 comments at the end of the survey in a "final comment" section, for a total of 309 comments from 485 participants. These comments helped shape the content of our Discussion.

Existence of this additional source of information was actually already mentioned in the first version of the paper (page 7, line 22-25 of original manuscript), but we did not specifically elaborate on that for reasons given above. As we now appreciate its importance, we have modified the manuscript to better reflect this point (page 7, lines 38-45).

Furthermore, we wish to take advantage of BMJ online features to append all these comments as "supplemental material" for readers' view.

As for the comment that we should have conducted focus group discussions to confirm and explore more deeply the indications emerging from the survey, we obviously agree that this is an important aspect in the process of making the best out of these data. In this respect, we wish to point out that the findings of our survey were thoroughly reviewed and discussed on several occasions. Within the whole research team, we did in-depth review among us through emails, teleconferences, and face-to-face meetings. In addition, on the occasion of a meeting of some of us with the European Federation of Pharmaceutical Industry Associations (EFPIA)'s clinical and regulatory task force of over 25 participants (Brussels, November 6th 2012), we had the opportunity to illustrate our results to a large panel of thought leaders, who made interesting comments relevant in further shaping our discussion. However, we are confident the reviewer will appreciate that due to embargo to unpublished information, the discussion was kept informal, and obviously it did not produce any material we can specifically quote.

This is now mentioned (page 7, lines 40-42 of revised manuscript).

We wish to thank the reviewer for the opportunity to clarify this important aspect, and we hope to have allayed reviewers' concerns about our having enough data to support the statements in the Discussion.

- Well done for tackling this issue - I do think it would be worth putting in some extra effort to add to

the data from the online surveys if you are able?

As mentioned, we are now submitting “free text” comments as online Supplemental Material.

IV. Response to reviewer Jacques Demotes Mainard

- The objective of the article “Factors Influencing Clinical Trial Site Selection in Europe: the SAT-EU StudyTM” is to identify the weight of different factors impacting European clinical trial site selection in various decrease areas for clinical trial in Europe since 2007.

- It shows that, for industry sponsored clinical studies, the main factors for selecting the European sites are investigator, networks, hospital and environment factors. Cost aspects seem to have less importance than expected. These data are of substantial interest for policymakers in Europe and help focus on the right parameters to improve the competitiveness of Europe in clinical research.

We wish to thank the reviewer for his praise to our work, and for the opportunity to improve its presentation. Further to his comments, the manuscript has been modified in several places, and additional new information is now provided.

We answer the various comments below.

Major points:

- Contrary to what is written in the article in the introduction (Line 58, page 5: « We also investigated whether trial selection needs differ between academic and commercial sponsors”.), it is clearly stated in the questionnaire that the survey is focused on industry-sponsored clinical research and indeed is not covering academic-sponsored studies.

Thus it should also be highlighted in the article that this survey and its results concerns only industry trials. Furthermore, it also impacts on the limitations of the survey. Academic sponsors could have different priorities (particularly in terms of costs vs. timelines) and correspond to a significant number of Clinical Trials in Europe.

We thank the reviewer for having spotted what actually is a mistake in wording in the introductory comments of the survey (not the manuscript).

We do appreciate and share the reviewer’s contention that academic sponsors manage a significant number of Clinical Trials in Europe, and could have specific priorities which may differ from those of commercial sponsors. In fact, our survey was aimed at obtaining information from both sides. However, we regret to admit that at one point in the overall introduction to the on line questionnaire it is (wrongly) said that the survey was focused on industry-sponsored clinical research.

We wish to be able to convince the reviewer that our survey was by no means intended to be limited to industry-sponsored clinical research, and that as said this was simply an unfortunate mistake, which had no practical consequences. In fact:

1. We included in the mailing several large organizations which do not typically participate in “industry sponsored” trials, such as the Medical Research Council Clinical trials Unit London (MRC CTU London), the European Clinical Research Infrastructure Network (ECRIN), The European Organization for Research and Treatment of Cancer (EORTC), and the Ireland Cooperative Clinical Research Group (ICORG).

2. In addition to private Clinical Research Organizations (CROs) we also contacted and obtained response by prestigious Academic Clinical Trials Units (CTUs) (e.g., Oxford University Diabetes Research Unit, Duke Clinical Research Institute, Harvard TIMI Group).
3. We were able to track the responses of individuals working for academic CTUs separately from the responses of Industry and of CROs. Interestingly, we found no statistically significant differences in their responses.
4. Most personal mailings were sent to academic investigators.
5. The survey itself concerned all clinical trials, regardless of possible industry sponsorship, as all questions were about trials in general.

Moreover, we wish to emphasize that actual survey questions only referred to “trial selection criteria for multi-center, hospital based trials” (questions 8-14), to “phase II-III trials”, to “Phase III-IV trials”, to “trials” or to “Multicenter RCTs” (questions 15-18). None of the questions, in any part of the survey, asked about “Industry-led trials” or “Industry-sponsored trials”.

Finally, in the survey itself (i.e., besides the introductory statement), the word “Industry” appears only when responders were asked to describe their professional profile, as can be easily verified by performing a word search of the whole questionnaire.

We hope we have been able to satisfactorily clarify this point.

- Results: It seems there are some discrepancies in responders: 20% are CTUs but the total of responders from CTU (i.e., Head of CTU or staff members from CTU in Fig. 3) corresponds to 33.8%. Please clarify.

We thank the reviewer for spotting this issue related to answers about organization and job title. We agree that there may seem to be a discrepancy in that respect, and we try to clarify this issue as follows:

These were actually 2 separate and independent questions. In the first question, respondents were asked to identify the organization to which they belonged, and indeed 22% of responders identified themselves as belonging to a CTU (Figure 3 right panel).

The second of these two questions, instead, was on job posting, and it was designed to gauge the hierarchy of respondents in order to estimate the contribution of people in management or top management positions (versus staff members). This has allowed us to identify for example that 304 participants (63%) were “Managers, Directors, VPs, Department Heads” from CTUs, CROs or Industry.

Of course, it is possible that some respondents may have misinterpreted the second question, with respect to the organization. In other words, having already answered the type of organization they belonged to, subsequently some of them may have just focused on their role within it, disregarding the type of organization. In retrospect, we now realize this part of the second question was redundant, and in fact potentially misleading.

Figure 3, left panel of the original manuscript (“Respondent’s Hierarchy”) has therefore been modified accordingly, focusing only on the position in the hierarchy. Information as to which type of organization a respondent belonged to is now summarized in new Figure 3 using data from the specific question and relative response, as shown in Figure 2 (“Respondent’s Organization”)

- In the text it is said that investigator- and hospital-dependent levers combined for early phase studies have a weight of 60/100, while it seems lower on the figure.

As per Managing Editor's request, Figure 4 of the original manuscript has been converted into a Table (new Table 2) and therefore it now clearly shows that investigator and Hospital dependent levers have a combined weight of 58.6 for early studies, and 57.4 for late studies

- Discussion: The different parts on the cost aspects in the overall article are ambiguous and too much insistent. Among the four levers it is shown to be the less important. But the results and the discussion focus on the government financial/tax incentives when cost of running trial is not discussed. After having insisted that the costs are less important than the other factors, it is highlighted that the hidden costs should be reduced.

Furthermore those hidden costs are indirect and could be considered as subjective, as an author interpretation rather than based on a specific question to the stakeholders.

We thank the reviewer for the opportunity to clarify this important point.

First of all, we wish to share with the reviewer that the results on costs came to as a surprise to us as well, as we started this project thinking that they would score very highly, as per "common wisdom". However, the data actually point to a different direction.

Our findings and related main discussion, is that the relatively high cost of running trials in Europe (vs lower-income countries, for example) seems to be significantly less crippling than the loss of time (and, hence, money) associated with bureaucracy, and delayed trial start. This is what we mean by "hidden costs", i.e., the money invested which will eventually get lost (or spent less efficiently) through lost time, failure/delay in patient recruits, excessive bureaucracy, and so on. This contention is actually directly supported by the many comments received by survey participants.

Just as an example, here are some comments provided as "free text" by our respondents reflecting this point (full disclosure of such comments is now available as on line supplemental material; see also our response to Dr. Trudie Lang, above):

- "For Phase II and beyond enrollment potential (with per patient costs already determined) drives almost every decision"
- "As for all studies (mainly Phase II and III) the biggest hurdle is the admin. time approval"
- "(More efficient centralized approval) "would help a lot: Save time. Save resources".
- "Direct cost is not the main driver as speed of enrollment has more impact on overall cost and it makes speed, both in start up phase and enrollment phase, the main driver"
- "The environment and costs probably contribute more to the country choice. In a given country the unit and investigator items are of the most relevance when choosing sites, as the budgets are generally consistent across sites"
- "Translations into local language are also a stopper when we are compared to English native speaking countries. IECs, RRAA should accept documents in English, which will save a lot of time and costs"

Furthermore, on the occasion of a meeting of some of us with the European Federation of Pharmaceutical Industry Associations (EFPIA)'s clinical and regulatory task force of over 25 participants (Brussels, November 6th 2012), we had the opportunity to illustrate the findings of our survey to a large panel of thought leaders, who made interesting comments which proved relevant in further shaping our discussion. We are confident the reviewer will appreciate that due to embargo to unpublished information, the discussion was kept informal, and obviously it did not produce any material we can specifically quote.

In other words, from stakeholders' feedback and from follow-up discussions, it would seem that to the extent that European sites may not be considered for a clinical trial, the likely culprit is the costs associated with excessive administrative time required to get a trial site up and running.

Thanking you for your comments, we have clarified the point about hidden costs under "discussion" Accordingly, we have qualified statements about hidden costs to address this point (Page 14, lines 37-48 of manuscript); in addition, conclusions have been made more cautious (see conclusion section page 17 lines 32-47)

- Some interpretations, in addition to the previous one, are too affirmative compared to the actual results:
- Discussion: On page 13: "Our survey clearly indicates that stakeholders would like a single "trial market". The sentence is too affirmative, the question is not clearly asked in the survey and thus rather reflects an interpretation by the authors
- Conclusion: "it requires harmonized national adoption" + "aligned hospital contracting" is not supported by the results.

We see the reviewer's point here, are grateful for such careful reading, and have adjusted the text to be less categorical about these statements (see Discussion section)

In this respect, however, we wish to underline that statements about "single market", "harmonized national adoption", and "aligned hospital contracting" (now toned down/caution added, see page 15 of the manuscript, lines 12-13) are supported by the very many comments we received on bureaucracy (see supplemental file). About half of all 309 comments were focused on bureaucracy and the need for alignment across the EU, such as:

- "Bureaucracy should be reduced in EU. One unique contract with the sites. One Central Europe Ethics Committee"
- "Central ethic committee approval is needed"
- "In my opinion the best is to have ONE EC approval for all sites participating in the multicenter clinical trials."
- "Better transparency of information regarding EC regulations, easier contracting with hospital, smooth authorization of clinical trial"
- "Central ethic committee approval is needed"
- "Approval times, IEC, Reg Authorities as well as financial contract signature are essential time periods for a quick start up. We need to improve this in Europe if we want to be competitive with other areas in the world. Despite the European Directive, the framework is not common, neither the timelines nor the documents required."
- "Main point: contracting process should be smoother"
- "Improvement in contracting process for clinical trials would be of great help"

Finally, the need to align contracting was among the most heavily emphasized recommendations received during the already mentioned external consultation held with EFPIA's clinical and regulatory task force.

Indeed, it is instructive to notice that the statement about a need for "harmonized national adoption" is also importantly supported by recent work of the European Commission (Brussels, July 17, 2012 COM(2012) 369 final), recommending among other things:

- A harmonised authorisation dossier, partly codifying the existing Commission guidance contained in EudraLex, Volume 10;
- A 'single portal' to submit an application for conducting a clinical trial linked to an EU database. This portal should be managed by the European Commission and be free of

charge for sponsors.

Minor points:

- Introduction: The objective is to assess the weight of different factors on the European clinical trial sites selection. The article starts with the observation of the decrease in clinical trials in Europe between 2007 and 2011 and what could have been the reason for such decrease, without hard evidence on the actual weight of those factors. But if the identification of the weight allows to improve the current situation, it won't directly explain and confirm, or not, the reasons for the decrease in the number of clinical trials in Europe. Maybe the sentence linked to the decrease in Europe should be reformulated to avoid the misunderstanding.

As per reviewer's request we have modified the Introduction in order to clarify this point (see Abstract Objectives on page 3 lines 14-17 of the revised manuscript)

- Methods: Survey design: How did you proceed for identifying the main criteria expected to impact site selection?

- "The defined criteria underwent review and discussion with a small number of knowledgeable professionals". What is this small number and most importantly how do you define "knowledgeable" professionals (what kind of position or experience...)?

As stated at page 6, line 32-34, of the original manuscript, a multi-stage approach was used to develop the survey, which began with a hypothesis development phase. First, the main criteria expected to impact site selection were tentatively identified in conference by the project team, who is composed by several investigators with broad and long-standing experience in the field of clinical trial conduct and site and country selection issue. Before setting up the actual survey to complete this process and validate our thinking, and to make sure that potentially relevant issues had not been missed. We took care of reviewing and discussing the criteria with knowledgeable colleagues outside the research team

We consulted in separate occasions with eight people, mostly from the Academic and CRO segments; "knowledgeable" is defined as individuals whose career is devoted to the development and execution of clinical studies, or who works in a healthcare environment which is totally reliant on clinical trials and clinical trial results.

We hope this explanation is satisfactory

- Remark: Rationale for having twice the costs in aspects, this could add a bias on the impact of this factor.

We respectfully disagree with the reviewer's contention on this issue. As already discussed, there seems to be a widespread (but unsubstantiated) perception that "costs" are what is driving clinical trial industry outside Western Europe. Thus, we felt they had to be weighed on repeated occasions to fully capture the "reality". Accordingly, first we asked about costs in the overall setting (costs vs. investigator vs. environment, vs. Hospital driven factors) for both early and late phase trials (as

defined in the question). We then assessed costs as part of the environment question, since running trials may be associated with different costs in the different countries.

We also wish to respectfully point out that the two aspects of costs were asked separately, and kept separate in terms of data analysis and presentation of results. Thus, there could be no statistical bias in that respect. The fact that we then talk about “costs” in the Discussion simply reflects the purpose of keeping the discussion relatively simple and straightforward.

We hope the reviewer and Editors will concur with this logic.

Methods:

It is not mentioned in the text how Biotech/Other/Medical Devices responses have been used as only CTU/CRO and Industry are described. Those 3 categories represent around 20% of the responders. Not clear in “responders demographic paragraph” (but distribution given in the figures).

Biotech and Medical device participants were batched with Industry. This was mentioned in the legend of figure 2 of the original manuscript, and it is now also detailed in the footnote of Figure 2 of the revised manuscript. “Other” was kept separate due to its mixed nature, again as stated in the legend of Figure 2. “Others” includes:

- Industry respondent working for a mixed portfolio company with either Pharma/Biotech portfolio or Pharm/Medical Device portfolio (self reported)
- Regulatory/Clinical Consultant
- Hospital or private clinic

- Results: 72% of question answered, i.e.? 485 responders (100%) concerns the identity, but N=341/342 for the different factors and N= 253/296 for the others questions, I am not sure to understand the distribution of the questions answered per person.

There were 485 respondents, 253 of whom answered all questions. The remainder of respondents chose not to respond to one or more questions, and therefore the overall response rate to each question is 72%. However, the questions left eventually unanswered could differ among incomplete responders, as each respondent chose autonomously which question reply to; hence, there may be a variable denominator for each single question. For the sake of clarity and transparency of information we decided to disclose also the number of respondents for each question. Example:

- 485 responders (100%) did answer the identity questions
- N=341/342 answered questions related to the various factors affecting trial site
- N= 253/296 answered the others questions

We hope we have satisfactorily addressed this concern.

- Results: The results on the desirability of running trials in the EU countries are, as described, a personal perception from the responders. It would be of interest to compare it to the number of studies performed in those countries (particularly with objective data), and if some discrepancies appear they should then be discussed.

We agree, and wish to thank the reviewer for having made this very important suggestion.

To address this issue, we ran a search through the official Web site Clinicaltrials.gov, looking for clinical trial distribution per country. The figure below shows a tight correlation ($r = 0.86$) between our

study's "trial desirability score" (x axis) and the number of trials in each country as found on Clinicaltrials.gov (y axis). (Note that since this figure may not be visible in the web upload format, it has also been uploaded as a supplemental file for editors only, labeled "SAT EU Trial Incidence Supplem Mat Editors)

- Results: The comparison of the importance of the different factors is regularly qualitative rather than quantitative. Mainly cost factor are often considered as significantly less important but the percentage of this factor is never given in the text (only to be estimated from the figure). It seems from the figure 4 that the costs factor is less important in the early stage compared to the late stage. Is this difference significant or not?

The reviewer is correct that actual data were not provided in the text, in part to avoid repetition and in part due to the 3'000 word restriction. However, as per a specific suggestion made by the Managing Editor , we have now changed Figures 4-7 of the original manuscript to Tables 2-5 with statistical outcomes and values provided.

. The reviewer is also correct that the cost data is less relevant in the early stage (16/100 versus 19/100). Please see new Table 2 replacing Figure 4, which has all of the relevant data and statistics.

We have also add data labels to remaining figures 2 and 4 to make data more easily readable

Results:

- I am not sure to understand the interest to pool investigator- and hospital- dependents levers.

These were pooled because they are the two criterions that the leadership in a Clinical Trial Unit can directly make decision about: costs are driven by the cost of supplies and salaries, while the environment is dictated by macroeconomic and regulatory factors and therefore less amenable to CTU management change. Pool investigator- and hospital- dependent levers are therefore the ones which a leader of a CTU is more likely to be able to influence.

We hope the reviewer will concur with us.

- In the description of the impact of two factors is missing (Presence of country on core country list and Hospital approval/contracting system) when the other 16 appear.

Data on these was omitted to keep the paper from getting too long. However, we will be willing and ready to add them if the Editors and reviewer wish so.

- Investigator driven criteria is always shown before the environment ones, except in the description in the results page 10. It would be better for the reader to keep the same order for the readers.

Agreed, we have switched these around. See pages 10-11 of revised manuscript under "Results"

- Discussion: By having the weight of the different factors it helps to improve the drawing power of the European sites. But it would be relevant to discuss the competitiveness with other countries.

We agree with the reviewer that the competitiveness with other countries is interesting. However, the survey was not designed to capture information outside Europe. This is an interesting suggestion, which could spur further research in the future.

- Limitations: Probably less impact but one part of the questionnaire concerns more specifically Italy and Cardiology. Could this be a bias, meaning that maybe the stakeholders involved in cardiology studies were more willing to respond to the survey?

The reviewer is correct that we also took advantage of this survey to append a few more questions which we hoped could be of help in understanding the cardiovascular environment in Italy for future analysis. However, we believe these questions (at the end of the survey) are unlikely to have influenced our results, since:

1. We invited individual respondents and stakeholder groups regardless of their disease-specific interest
2. Within large organizations, the survey was eventually passed on the ultimate respondents based on their involvement in running clinical trials, not based on specific questions (which in fact were accessible only to those who actually entered the survey)
3. Same is true for individual respondents who found the survey advertised on social networks or Web sites, without prior access to questions
4. Of those who did perform the survey, many left those questions blank; some also went on to comment as free text "not able to answer".

- The result of the question (in the survey) on the rating of the countries depending on the availability of equipment doesn't appear in the article. Is there any reason?

Correct. Given the limited space we opted to omit as less interesting. This also stems from the consideration that, aside for some very peculiar phase II trials which may require a specific equipment (e.g., cardiac MRI, mass spectroscopy for metabolomics...), the great majority of randomized clinical trials, due to their very nature of trying to be as inclusive as possible, rely on use of technology available to most hospitals in Europe..

However, we will be ready and willing to include if Editors and reviewer wish so.

- Figure 8: lower panel: N=253 as well as the previous panel?

Both panels reflect the same sample size, which actually is 296 respondents

- Ref 12: should refer directly to the EU press release rather than to the EFPIA site that refers to it for the decrease in the number of clinical trials in Europe between 2007 and 2011.

Thank you for the comment; we have modified reference 12 accordingly,

In summary: acceptable pending on appropriate modifications

VERSION 2 – REVIEW

REVIEWER	Demotes Mainard, Jacques INSERM
REVIEW RETURNED	26-Sep-2013

GENERAL COMMENTS	<p>The authors have taken into account the comments and clarified several aspects. The article has improved as the conclusion is now better aligned with the results, avoiding over-interpretation.</p> <p>However, some issues remains:</p> <p>1 - I am not completely convinced by the argument given by the authors concerning the minor impact of the mistake in the wording in the introductory comments of the survey. Even though most respondents work both on the academic and industry sides, the CTU participating in the survey may have understood that they should restrict their responses to the industry trials, thus introducing a possible bias.</p> <p>2 - Could the author provide an explanation for the discrepancies in the data on CTUs personnel (33.8% are “heads of CTUs” or “staff members in CTUs” but only 20% considered they are working in a CTU). I agree with the modification of the diagram, but I would prefer to get a more suitable explanation or description of the discrepancy.</p> <p>3 – We suggest the authors should provide the figures regarding « hospital approval / contracting system », since this refers to an important point in the discussion on administrative burden.</p> <p>4 – Could the authors double-check the sample size in Figure 8 ?</p>
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VERSION 2 – AUTHOR RESPONSE

Response to Reviewer: Jacques Demotes Mainard

The authors have taken into account the comments and clarified several aspects. The article has improved as the conclusion is now better aligned with the results, avoiding over-interpretation.

We thank the reviewer for his appreciative comments regarding our revision of the manuscript. Here we offer our reply to the additional questions.

1 - I am not completely convinced by the argument given by the authors concerning the minor impact of the mistake in the wording in the introductory comments of the survey. Even though most

respondents work both on the academic and industry sides, the CTU participating in the survey may have understood that they should restrict their responses to the industry trials, thus introducing a possible bias.

As already discussed, our survey was by no means intended to be limited to industry-sponsored clinical research. This is testified by the fact that none of the questions -in any part of the survey- asked about "Industry-sponsored trials", and by the large number of responses drawn by individuals working in not-for-profit organizations or academic trial units.

However, in keeping with the reviewer's concern, we have added a sentence in the Limitations section to this effect (see manuscript page 15 line 58 to page 16 line 7)

2 - Could the author provide an explanation for the discrepancies in the data on CTUs personnel (33.8% are "heads of CTUs" or "staff members in CTUs" but only 20% considered they are working in a CTU). I agree with the modification of the diagram, but I would prefer to get a more suitable explanation or description of the discrepancy.

We are glad to hear that the reviewer is pleased with the way we present this information in Figure 3.

At the same time, though, we are sorry if we cannot be more accurate in providing an explanation as to why some respondents may have mistakenly misinterpreted the second question, with respect to their working organization.

As already discussed, we can only infer that, having already answered which type of organization they belonged to, some of the respondents may have subsequently just focused on their role within their organization. In other words, for the subsequent questions some of them may have just taken for granted that their answers would refer to the type of organization they initially identified as belonging to.

We do realize that this is only an indirect explanation, unsupported by direct insights. However, we are confident that Editors and reviewer would concur with us that it is hard to imagine the precise intimate reasoning that takes places in the mind of respondents when faced with a specific question dealing with their own job description: this is something only the very person answering the question can judge, and therefore we must take those answers at their face value.

Also, we honestly do not see how delving even deeper in respondents' job description would impact the type of data gathered and the conclusions reached. Finally, we must admit that we wouldn't feel proficient enough to correctly describe this issue in a clear and concise way.

For all those reasons, we would prefer not to further change the manuscript. However, we will be happy to introduce a sentence to that effect if the Editors or the reviewer would be willing to help us with crafting a proper statement that could effectively deal with this issue.

3 – We suggest the authors should provide the figures regarding « hospital approval / contracting system », since this refers to an important point in the discussion on administrative burden.

We agree this question on administrative burden is important.

Table 5 "Hospital-driven criteria in selection of phase II-III trial sites" shows these data. Specifically, Hospital approval/contracting system ranks 4th out of 6 factors with respect to the impact on clinical trial site selection process.

4 – Could the authors double-check the sample size in Figure 8?

Actually, we do not have a figure 8, as can be seen in the PDF of the uploaded manuscript. We do have an attachment #8 in the BMJ Open database, which corresponds to Table 2 of revised manuscript (Levers impacting trial site selection for early and late trials). If this is what the reviewer is referring to, we have double checked, and N= 341.