# Trial Extension Studies (TES) in Rheumatology

Dear Taskforce Member,

Please find below the second survey on the design and reporting of Trial Extension Studies (TES) as part of your task as a panel member.

In the first survey it was suggested that the length of an extension study varies and may depend on the length of the previous RCT; for example, an extension study following a short RCT would not necessarily be a long-term study. Accordingly, we have renamed ‘Long-term Extension Studies’ into ‘Trial Extension Studies’.

In this survey you will be provided with the results of the first survey which you can view before answering each question. Please read them carefully before answering the new question. There will also be the opportunity to include free text and comments to almost all the questions.

We would like to emphasise that there are no absolute wrong or right answers. The survey is reasonably detailed and is likely to take approximately 30 minutes to complete. Please make sure that you do not leave the survey half completed.

This survey is not anonymised - at the end of the survey, we will ask you for your email address in order to be able to send you additional information +/- feedback of your answers to this survey if indicated.

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## Trial Extension Study (TES) Taskforce

### 1. PARTICIPANTS

**In the first survey, we asked your opinion on involvement in the taskforce by representatives of industry, regulatory agencies (FDA, EMA) and contract research organisation (CRO). The responses were as follows:**

**A) Industry representative: 25% no involvement, 19% limited, 44% some, and 13% full.**

**B) FDA/EMA representative: 6% limited, 50% some, and 44% full.**

**C) CRO representative: 19% no involvement, 31% limited, and 50% some.**

**There is general agreement for some level of particpation; therefore as a minimum, we will try to have a representative from the above mentioned bodies to provide comments on the final document; however, please rate your level of agreement for the following (0 = none to 10 = maximum)...**

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| having an industry representative providing comments on one or more drafts | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| having an administration (FDA, EMA) representative directly participating in the taskforce | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| having a CRO representative providing comments on one or more drafts | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

## 2. ITEMS TO BE INCLUDED IN THE FINAL DOCUMENT

**Following your responses, the following items are to be included in the final document:**

**• A reference to the STROBE guidelines for reporting observational studies (mean agreement 9.3/10)**

**• A definition of TES studies (mean 9.7)**

**• A paragraph on the strengths and limitations of TES Studies (mean 9.1)**

**• A checklist with the minimal dataset a study should collect (mean 9.4)**

**• Recommendations on how to build a flow chart of the study (mean 8.4)**

**• Recommendations on how to analyse the data (mean 9.1)**

**• Recommendations on how to report the results (mean 9.2)**

**• Ethical comments (mean 7.9)**

**Do you agree with adding all the above items?**

- ○ Yes
- ○ No

If no, please explain why

## Definition of a TES

### 3. STUDY DESIGN DEFINITION

**From the responses in the first round, no single definition for a TES proved to be satisfactory; please see the responses below:**

**"A TES may be a study that...**

**• ...follows patients beyond the pre-specified RCT period (mean 7.1)**
**• ...follows patients beyond the pre-specified RCT period, on condition that all patients entering the original trial are accounted for (mean 7.9)**
**• ...follows a placebo-controlled study (mean 5.0)**
**• ...follows an active-comparator study (mean 5.1)**
**• ...follows a placebo-controlled study in which patients start the experimental treatment either as a result of randomised allocation or crossover after placebo treatment; and only patients on experimental treatment are followed beyond the pre-specified trial period (mean 4.6)**

**We felt the best and most comprehensive definition was (mean 7.7):**

**"A TES may be a study that follows all patients beyond the pre-specified trial period whether the trial was:**

**A) a placebo-controlled RCT with the possibility to cross-over to open label drug;**

**B) OR a placebo-controlled RCT with the possibility to cross-over to usual care;**

**C) OR an active comparator trial "**

**Do you agree with the above definition?**

- ○ Yes
- ○ No

If no, please explain why

## 4. STARTING POINT OF A TES

**No clear definition of what constitutes the starting point of a TES emerged from the first round responses. We have added further options which we would like you to answer. Note that choosing a definition of the starting point does NOT imply data preceding that point should not be reported.**

**Which of the following options would you choose as the start point of a TES? (Choose only one)**

- ○ Start is on completion of the pre-specified RCT period (1st round 46% in favour)
- ○ Start is at the point of cross-over or switch of therapy as allowed in the RCT (1st round 54% in favour)
- ○ The start of the TES is the start of the extension trial (new item)
- ○ The start of the TES depends on the research question (new item)

If you chose the last option, please specify:

## 5. LENGTH OF A TES

**In the first round, most respondents supported not defining a minimum period of a TES (47%), and 40% voted for a period exceeding 3 years. Only 7% favoured up to 12 months and 25-36 months and no-one supported 13-24 months. We would like you to answer the following (which includes some additional items).**
**Which of the following options would you choose as the appropriate length of a TES? (Choose only one)**

- ○ More than 3 years (1st round 40% in favour)
- ○ At least 5 years (new item)
- ○ The minimum length of a TES need not be defined (1st round 47% in favour) as the length of a TES depends on the research question (new item)

If you chose the last option, please specify:

## Population

**6. From responses in the first round, a single definition for the population to be included in a TES could not be decided. The responses were as follows:**

**"The population of a TES…**

**• Should include all patients initially included in the RCT (mean 9.1)**
**• Should include only those patients who achieved remission during the RCT (mean 2.0)**
**• Should include only those patients who achieved remission or a low disease-activity (LDA) state during the RCT (mean 2.8)**
**• May include patients with any level of disease activity on completion of the RCT (remission, LDA or moderate-high disease activity) (mean 7.4)**
**• Should not be defined upfront for all TES (suggested new item)**

**The best definition from feedback would seem to be:**

**"The population of a TES should not be defined in a guideline since it depends on the research question; but it should preferably include all patients initially included in the RCT (with the ability to separately report on patients with specific area of interest e.g. remission, LDA etc) "**

**Do you agree with the above definition?**

- ○ Yes
- ○ No

If no, please explain why

## Potential challenges

**7. Following the responses from the first round , the following items are to be included in the final document:**

**• Rare safety events may not be detected for reasons other than the length of observation (mean 7.8)**

**• Since TES are largely supported by pharmaceutical companies, the potentially limited access to data linkages (which are important for long-term observations) may further question the overall benefits of such studies (mean 7.1)**

**• Even if all patients in a RCT were entered into a TES, such a study is generalisable only to patients with similar disease characteristics; many trial populations do not reflect patients seen in routine care (mean 7.8)**

**• The definition of comparator groups in a TES may be difficult because of the absence of a clear null hypothesis (mean 7.4)**

**• Unwanted heterogeneity may result by wishing to accommodate countries where treatment options may be more limited (e.g. allowing patients with higher levels of disease activity to be recruited where otherwise inclusion is of patients in remission/LDA state only) (mean 7.6)**

**Do you agree with adding all of the above items?**

- ○ Yes
- ○ No

If no, please explain why

**8. One participant suggested the following in the first round:**

**It is desirable that TES are performed independently from companies (suggested new item)**

**How strongly do you agree with adding this item to the final document?**

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Space for comments

**9. POTENTIAL SOURCES OF BIAS OR LACK OF GENERALISABILITY OF TES**

**From the responses in the first round, the following items are to be included in the final document:**

**"The inclusion of patients in a TES following completion of a RCT…**

**• …usually requires a certain level of response (mean 7.9)**

**• …may be influenced by the fact that the investigator is remunerated for each patient recruited (mean 7.4)**

**• …may be influenced by geographical differences in practice / approach (leading to differences in number and nature of patients included) (mean 7.5)**

**• …may be influenced by the stage of the disease of the patient (mean 7.0)**

**Do you agree with adding all the above items?**

○ Yes

○ No

If no, please explain why

## Objectives of TES

### 10. SAFETY

**From the responses in the first round, the following items are to be included in the final document:**

**"A trial extension study…**

**• …may identify new adverse effects that the original RCT was not able to detect due to greater cumulative exposure to the drug (mean 8.4)**

**• …is not powered for rare adverse events and so should not be relied upon to detect safety signals (mean 7.6)**

**• …may identify whether the incidence of known adverse effects show change with longer-term drug exposure (e.g. infection risk) (mean 7.5)**

**• …may confirm whether the nature of known adverse effects identified from the RCT changes with longer-term exposure (e.g. infection risk) (mean 7.6)**

**• …is inappropriate to detect rare safety events due to the inclusion of a selected population (responders with likely no previous adverse events) (mean 7.0)**

**Do you agree with adding all the above items?**

- ○ Yes
- ○ No

If no, please explain why

## 11. EFFICACY

**From the responses in the first round, the following items are to be included in the final document:**

**• The greater cumulative exposure of the active drug in a TES may identify additional information on the drug's efficacy (mean 6.9)**

**• A TES may allow evaluation of relapse including time to relapse (for example, patients entering the TES having achieved an acceptable state, such as LDA or remission, on the active drug can be followed to assess sustainability) (mean 7.8)**

**Do you agree with adding these items?**

- ○ Yes
- ○ No

If no, please explain why

## 12. ADDITIONAL OUTPUTS

**The responses from the first round regarding the additional outputs that a TES may provide were not conclusive. Indeed, there were more responses in the "disagree" or the "uncertain" area than "in favour" as shown below:**

**Besides efficacy and safety, and despite a clear scientific benefit, a TES may allow…**

- **…economic evaluation of long-term treatment with the active drug (mean 6.3)**
- **…better Health-related quality of life (QoL) analysis (mean 6.5)**
- **…better evaluation of the risk-benefit ratio and therefore overall advantage of the drug (mean 6.9)**
- **…information about compliance (suggested new item)**

**As a result, the introductory statement has been changed from "may allow" to "may also address". Please answer now:**

**For the following statements on justifiable outcomes of a TES, please grade your level of agreement (0= none to 10= maximum)**

**Besides efficacy and safety, and despite a clear scientific benefit, a TES may also address…**

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ...economic evaluation of long-term treatment with the active drug | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...better Health-related quality of life (QoL) analysis | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| ...better evaluation of the risk-benefit ratio and therefore overall advantage of the drug | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| …information about compliance (new item) | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

## Minimal information

**13. From the responses in the first round, the following minimal information a TES should collect will be included in the final document:**

**• The time of last observation (mean 9.5)**

**• The functional status at the time of inclusion in the TES (mean 8.8)**

**• The functional status at last observation (mean 8.3)**

**• The disease activity at the time of inclusion in the TES (mean 9.3)**

**• The disease activity at last observation (mean 9.4)**

**• The reason for exclusion from the TES if the patient discontinues the drug (mean 8.8)**

**• The reason for cessation of follow-up (mean 9.4)**

**• Specification of reasons for cessation of follow up other than adverse event or inefficacy, e.g. geographical or doctor related reasons (mean 8.7)**

**• The progress at each stage from RCT start to TES completion (mean 8.7)**

**• The duration of active treatment (mean 9.5)**

**Do you agree with adding all the above items?**

- ○ Yes
- ○ No

If no, please explain why

**14. A participant in the first round suggested the following items be added to the minimal information a TES should collect. Please state your level of agreement (0= none to 10= maximum):**

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| The co-medication at each stage from RCT start to TES completion | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| The serious adverse events and any outcome related to safety at each stage from RCT start to TES completion | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**15. From the responses in the first round, the following item will be included in the final document:**

**"The minimum data requirements for TES following placebo- and active-controlled trials are the same." (93% in favor)**

**Do you agree with adding the above item?**

- ○ Yes
- ○ No

If no, please explain why

## Follow-up

**16. From the responses in the first round, the following item is to be included in the final document:**

**"A TES that follows an active-comparator RCT should follow all randomised patients for the same period of time (not only patients on the experimental treatment)" (mean 7.9)**

**Do you agree with adding the above item?**

- ○ Yes
- ○ No

If no, please explain why

## Analysis

**17. From the responses in the first round, with most of the items strongly supported, the following statements regarding the minimal information that a TES should collect are to be included in the final document:**

**• The null hypothesis should be stated at the start (mean 7.9)**

**• Multiple comparisons should be taken into account when determining the level of statistical significance (mean 8.1)**

**• The report should include details on how data for sustained effect was analysed (mean 9.4)**

**• The plan for subjects that drop out of a TES should be specified (mean 8.9)**

**• In a TES, the planned analysis of data to evaluate for sustained effect should be non-inferiority in nature (mean 7.6)**

**• The analysis of the data from a TES in rheumatoid arthritis (RA) should include the area under the curve of absolute disease activity (i.e. not response/change) preferentially expressed as a score (DAS, SDAI, etc.) (mean 7.3)**

**• The analysis should include survival / retention rates (mean 8.9)**

**• A TES should preferably include hard endpoints (e.g. death, work disability, joint replacement surgery, hospital admission) from linkages with other data sources (mean 8.6)**

**• The analysis of the data from a TES should take into account the dropouts (mean 9.3)**

**Do you agree with adding all the above items?**

- ○ Yes
- ○ No

If no, please explain why

**18. Two additional items were not clearly supported, although by the comments made and number of non-responses, the statements may not have been clear to the participants.**

**• The null hypothesis must be related to the results achieved in the original RCT. (mean 6.3)**

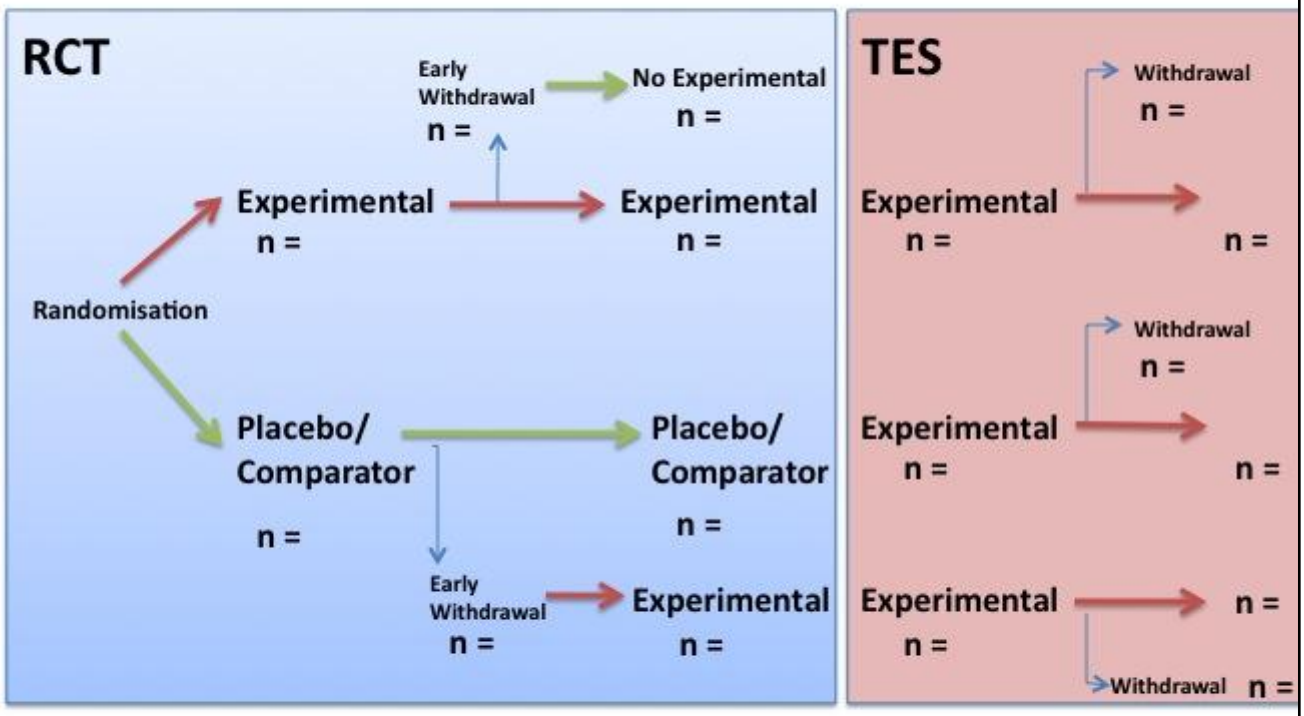
**• The analysis should include a pooled analysis from the original trial groups. (mean 6.4)**

**The items have therefore been re-phrased as below. Please rate your level of agreement with the following items (0 = none to 10 = maximum:**

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| The null hypothesis should take account of the results of the original RCT. Depending on the research question, the results of a RCT should be accommodated in the TES. | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| The report should comment on cumulative outcome analysis (beneficial and adverse events) maintaining the original trial groups i.e. from RCT start, not TES start to avoid reporting of only the sub-selected patient group that proceeds onto the TES. | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

## Flowchart

### New proposal of flowchart




Patients randomised to either group of the RCT may leave the trial early. Patients on the active arm may continue receiving the experimental drug until the end of the RCT or discontinue it before ending. Patients on the placebo/comparator group may continue on placebo/comparator until the end of the RCT or start on the experimental drug before the end of the RCT. At the start of the extension period two subgroups may therefore be receiving the experimental drug; in addition, those continuing in the placebo/comparator arm may also commence experimental drug if they enter the TES phase. During the TES, patients may continue receiving the experimental drug or discontinue it before completion.

**19. From the responses in the first round, the following item is to be included in the final document:**

**"All TES reports must include a flowchart on the progress of patients included" (mean 9.9)**

**The previous flowchart (agreement mean 9.3) has been improved following participants' comments: specifically the number of withdrawals during the TES has been added and some of the groups re-labelled.**

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Please rate your level of agreement with the revised flowchart (0 = none to 10 = maximum) | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

Comments

## Reporting of TES

**20. From the responses in the first round, it has been decided that the taskforce should develop and detail minimal standards that should be included when reporting a TES by means of a checklist (mean 9.2)**

**The following items are to be included in the final document:**

**• "The report of a TES should be consistent with and consolidate existing established guidelines including CONSORT and STROBE" (mean 9.4)**

**• The report of a TES should be consistent with the ACR/EULAR recommendations on the reporting of clinical trials in RA (Aletaha D, et al 2008) (mean 8.9)**

**• A report of a TES should include a flow diagram detailing numbers at each relevant time-point (mean 9.5)**

**• For those patients entering the TES having achieved LDA or remission during the RCT, the sustainability of such disease states should be evaluated and made available (mean 8.6)**

**• For those subjects that enter a TES not having achieved remission/acceptable disease activity state following the RCT, the number that achieve this during the TES should be reported – to determine whether longer drug exposure has the potential to improve disease state of such subjects further (mean 8.3)**

**• The drop-out rates from each arm during the original RCT and the cross-over groups should be available (mean 9.3)**

**• All drop-outs should be detailed (mean 9.1)**

**Do you agree with adding all the above items?**

- ○ Yes
- ○ No

If no, please explain why

**21. A participant in the first round suggested the following item be added:**

**• TES do not need to provide the same information for all randomised patients in terms of quantity and quality, irrespective of the nature of prior RCT, but should provide a minimum dataset (still to be defined) for the patients not followed in detail. Additional information, depending on the research question, is desirable but not mandatory.**

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| How strongly do you agree with adding this item (0 = disagree to 10 = fully agree)? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

## Nature and frequency of reports

**22. From the responses in the first round, we have concluded that the taskforce document should comment on the frequency (mean 7.6) and nature (mean 8.0) of the reports of TES.**

**Regarding the nature of reports, the following statements are to be included in the final document:**

**• The results of efficacy and safety of a TES should be reported together (mean 8.8)**

**• The credibility of split reporting (e.g. one abstract on efficacy, one on safety, one on QoL etc) – is questionable and should be discouraged by abstract selection committees and journal editors (mean 8.7)**

**Do you agree with adding all the above items?**

- ○ Yes
- ○ No

If no, please explain why

**23. A participant in the first round suggested the following item be added:**

**"The results of the groups of patients in different disease states should be reported separately"**

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| How strongly do you agree with adding this item (0 = disagree to 10 = fully agree)? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**24. Regarding the frequency of reports, the responses were not clear or not supportive of any specific alternative:**

**• The results of a LTE study should be reported every year (mean 4.2)**

**• The results of a LTE study should be reported every two years (mean 4.9)**

**• The results of a LTE study should be reported every three years (mean 5.4)**

**• The results of a LTE study should be reported annually to a maximum of 5 years (mean 5.4)**

**The following statement has therefore been decided to be included in the final document:**

**“The reporting frequency should not be specified for all TES since it depends on the research question. However, the protocol of each TES should specify the frequency of reports to be written and a reason for it (purpose, outcomes, length of RCT, etc).”**

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| How strongly do you agree with adding this item (0 = disagree to 10 = fully agree)? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

## Ethical issues

**25. From the responses in the first round, the following items are to be included in the final document:**

**• All of the subjects undergoing a RCT should be informed of the importance of long-term surveillance and be given the opportunity of entering in the long-term follow-up (mean 9.4)**

**• The subjects included in a TES should sign a new informed consent form (different from the one for the RCT) for continuation of data collection (mean 7.6)**

**And the following item is to be deleted:**

**• The subjects included in a TES should sign a new informed consent for continuation of drug (mean 5.9)**

**Do you agree with the above changes?**

- ○ Yes
- ○ No

If no, please explain why

**26. In addition, a participant in the first round suggested the following item be added:**

**• There is no need to update the consent of patients included in a TES annually, particularly since each additional consent runs the risk of additional drop-out**

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| How strongly do you agree with adding this item (0 = disagree to 10 = fully agree)? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

## Details

**27. We wish to be able to send responses to participants directly as may be indicated; therefore, please include your e-mail address below:**