Long-term extension (LTE) studies in Rheumatology

Dear Taskforce Member,

Please find below a survey on the design and reporting of long-term extension (LTE) studies as part of your task as a panel member.

The two main objectives of the survey are:

1. To define the items that should be included in a recommendation document.

2. To establish the level of agreement of statements in the document.

Your considered opinion is crucial to the successful outcome of this project.

Please read each section carefully before answering. You will be asked to answer specific questions (with graded response). There will also be the opportunity to include free text and comment.

We would like to emphasise that there are no absolute wrong or right answers. At the end of the survey, you will have available an open-ended box for comments.

The survey is reasonably detailed and is likely to take 30 minutes to complete. Please make sure that you do not leave the survey half completed.

If you do not feel sufficiently familiar or confident to answer any of the questions, please leave it blank.

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Aspects to be dealt with in the taskforce

1. How important do you feel it is for opinions of each of the following stakeholders to be included in the taskforce final document?

Please choose the most appropriate form of involvement for each individual

	None	Offer to provide comment on the final document	Offer to provide comment on one or more drafts	Participation in the taskfore
An industry representative	○	○	○	○
An administration (FDA, EMA) representative	○	○	○	○
A contract research organisation representative	○	○	○	○

Other (please specify)

2. How important do you feel it is for each of the following items to be included in the taskforce final document?

Please grade the level of priority or importance (0 = very low; 10 = extremely important)

	0	1	2	3	4	5	6	7	8	9	10
A reference to the STROBE guidelines for reporting observational studies	○	○	○	○	○	○	○	○	○	○	○
A definition of LTE studies	○	○	○	○	○	○	○	○	○	○	○
A paragraph on the strengths and limitations of LTE Studies	○	○	○	○	○	○	○	○	○	○	○
A checklist with minimal data the study should collect	○	○	○	○	○	○	○	○	○	○	○
Recommendations on how to build a flow chart of the study	○	○	○	○	○	○	○	○	○	○	○
Recommendations on how to analyse the data	○	○	○	○	○	○	○	○	○	○	○
Recommendations on how to report the results	○	○	○	○	○	○	○	○	○	○	○
Ethical comments	○	○	○	○	○	○	○	○	○	○	○

Are there other items or aspects that the taskforce / document should address?

Long-term extension (LTE) studies in Rheumatology

Definition of a long-term extension (LTE) study

The definition of a LTE study is in itself not clear and remains to be established. Several areas warrant consideration when determining the definition, such as design, length of study and the population that should be studied.

For the following statements on the definition of a LTE study, please grade your level of agreement (0 = none to 10 = maximum).

3. STUDY DESIGN DEFINITION

Please rate your level of agreement (0 = none; 10 = maximum)

(Options may overlap)

"A long-term extension study is any study that..."

	0	1	2	3	4	5	6	7	8	9	10
...follows patients beyond the pre-specified RCT period	○	○	○	○	○	○	○	○	○	○	○
...follows patients beyond the pre-specified RCT period, on condition that all patients entering the original trial are accounted for	○	○	○	○	○	○	○	○	○	○	○
...follows a placebo-controlled study	○	○	○	○	○	○	○	○	○	○	○
...follows an active-comparator study	○	○	○	○	○	○	○	○	○	○	○
...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	○	○	○	○	○	○	○	○	○	○	○
...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; OR B) a placebo-controlled RCT with the possibility to cross-over to usual care; OR C) an active comparator trial	○	○	○	○	○	○	○	○	○	○	○

Can you think of a better definition of the design of a LTE study? If so, please include free text in the box below

4. MINIMUM LENGTH of LTE STUDY

Towards defining the minimum length of a long-term extension study, which of the following 2 options would you choose as the starting point of a LTE study?

- ○ Start is on completion of the pre-specified RCT period
- ○ Start is at the point of cross-over or switch of therapy as allowed in the RCT

5. Using your preferred starting point, how many YEARS should a LTE study last?

- ○ up to 12 months
- ○ 13-24 months
- ○ 25-36 months
- ○ More than 3 years
- ○ The minimum length of an LTE need not be defined

Combining questions 4 and 5, can you think of a better definition of the length of a LTE study? If so, please include as free text in the box below

Patients that should be included in a LTE

6. PATIENT POPULATION

What patient population should a LTE study inform us on and therefore be included in such a study?

Please rate your level of agreement with the following statements (0 = none; 10 = maximum)

	0	1	2	3	4	5	6	7	8	9	10
Should include all patients initially included in the RCT	○	○	○	○	○	○	○	○	○	○	○
Should include only those patients who achieved remission during the RCT	○	○	○	○	○	○	○	○	○	○	○
Should include only those patients who achieved remission or a low disease-activity (LDA) state during the RCT	○	○	○	○	○	○	○	○	○	○	○
May include patients with any level of disease activity on completion of the RCT (remission, LDA or moderate-high disease activity)	○	○	○	○	○	○	○	○	○	○	○

Can you think of a better definition of the patient population that should be included in a LTE study? If so, please include as free text in the box below

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Potential problems of LTE studies

LTE studies raise other issues and concerns that may also be worth including in the final document.

7. For each of the following statements illustrating POTENTIAL CHALLENGES of a LTE study, please grade your level of agreement to mention in the final document (0 = none to 10 = maximum)

	0	1	2	3	4	5	6	7	8	9	10
Rare safety events may not be detected for reasons other than the length of observation	○	○	○	○	○	○	○	○	○	○	○
Since LTE 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	○	○	○	○	○	○	○	○	○	○	○
LTE studies may be extremely costly making them difficult to justify	○	○	○	○	○	○	○	○	○	○	○
Even if all patients in an RCT were entered into an LTE, such a study is generalizable only to patients with similar disease characteristics; many trial populations do not reflect patients seen in routine care	○	○	○	○	○	○	○	○	○	○	○
The definition of comparator groups in a LTE study may be difficult because of the absence of a clear null hypothesis	○	○	○	○	○	○	○	○	○	○	○
Unwanted heterogeneity may result by wishing to accomodate 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)	○	○	○	○	○	○	○	○	○	○	○

If you believe there may be other challenges with a LTE study that have not been mentioned and would be worth including in the document, please list them below

8. The following statements illustrate potential SOURCES OF BIAS OR LACK OF GENERALISABILITY of a LTE study.

Please grade your level of agreement to mention in the final document (0 = none to 10 = maximum)

The inclusion of patients in a LTE study following completion of a RCT...

	0	1	2	3	4	5	6	7	8	9	10
...usually requires a certain level of response	○	○	○	○	○	○	○	○	○	○	○
...may be influenced by the fact that the investigator is remunerated for each patient recruited	○	○	○	○	○	○	○	○	○	○	○
...may be influenced by geographical differences in practice / approach (leading to differences in number and nature of patients included)	○	○	○	○	○	○	○	○	○	○	○
...may be influenced by the stage of the disease of the patient	○	○	○	○	○	○	○	○	○	○	○

If you believe there may be other sources of bias in a LTE study that have not been mentioned and would be worth including in the document, please list them below

Long-term extension (LTE) studies in Rheumatology

Objectives or potential uses of LTE studies

The investigative objective of LTE studies may not be clear to many observers.

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

9. SAFETY

A long-term extension study...

	0	1	2	3	4	5	6	7	8	9	10
...may identify new adverse effects that the original RCT was not able to detect due to greater cumulative exposure to the drug	○	○	○	○	○	○	○	○	○	○	○
...is not powered for rare adverse events and so should not be relied upon to detect safety signals	○	○	○	○	○	○	○	○	○	○	○
...may identify whether the incidence of known adverse effects show change with longer-term drug exposure (e.g. infection risk)	○	○	○	○	○	○	○	○	○	○	○
...may confirm whether the nature of known adverse effects identified from the RCT changes with longer-term exposure (e.g. infection risk)	○	○	○	○	○	○	○	○	○	○	○
...is inappropriate to detect rare safety events due to the inclusion of a selected population (responders with likely no previous adverse events)	○	○	○	○	○	○	○	○	○	○	○

10. EFFICACY

	0	1	2	3	4	5	6	7	8	9	10
The greater cummulative exposure of the active drug in an LTE study may identify additional information on the drug's efficacy	○	○	○	○	○	○	○	○	○	○	○
A LTE study may allow evaluation of relapse including time to relapse (for example, patients entering the LTE study having achieved an acceptable state, such as LDA or remission, on the active drug can be followed to assess sustainability)	○	○	○	○	○	○	○	○	○	○	○

11. ADDITIONAL OUTPUTS

Besides efficacy and safety, an LTE may allow...

	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	○	○	○	○	○	○	○	○	○	○	○

12. In addition to the list above, what other outcomes do you think a LTE study may be able to identify?

Please include your comments in the box below

Minimum amount of information a LTE study should include

This next section focuses on specific recommendations related to the conduct of LTE studies.

13. The following items are proposals for the minimal information a LTE study should collect.

Please grade your level of agreement (0 = none to 10 = maximum)

	0	1	2	3	4	5	6	7	8	9	10
The time of last observation	○	○	○	○	○	○	○	○	○	○	○
The functional status at the time of inclusion in the LTE	○	○	○	○	○	○	○	○	○	○	○
The functional status at last observation	○	○	○	○	○	○	○	○	○	○	○
The disease activity at the time of inclusion in the LTE	○	○	○	○	○	○	○	○	○	○	○
The disease activity at last observation	○	○	○	○	○	○	○	○	○	○	○
The reason for exclusion from the LTE study if the patient discontinues the drug	○	○	○	○	○	○	○	○	○	○	○
The reason for cessation of follow-up	○	○	○	○	○	○	○	○	○	○	○
Specification of reasons for cessation of follow up other than adverse event or inefficacy, e.g. geographical or doctor related reasons	○	○	○	○	○	○	○	○	○	○	○
The progress at each stage from RCT start to LTE completion	○	○	○	○	○	○	○	○	○	○	○
The duration of active treatment	○	○	○	○	○	○	○	○	○	○	○

In addition to the list above, what other data do you think should be collected as a minimum requirement? Please provide comments in the box below:

14. Do you think the minimum data requirements should be different depending on whether the LTE study has followed a placebo-controlled or an active comparator trial?

- ○ Yes
- ○ No

If you answered 'yes', please describe what should be different.

15. FOLLOW-UP

Please grade your agreemenent with the following statement (0=none, 10= maximum)

	0	1	2	3	4	5	6	7	8	9	10
An LTE study that follows an active-comparator RCT should follow all randomised patients for the same period of time (not only patients on the experimental treatment)	○	○	○	○	○	○	○	○	○	○	○

Analysis and interpretation

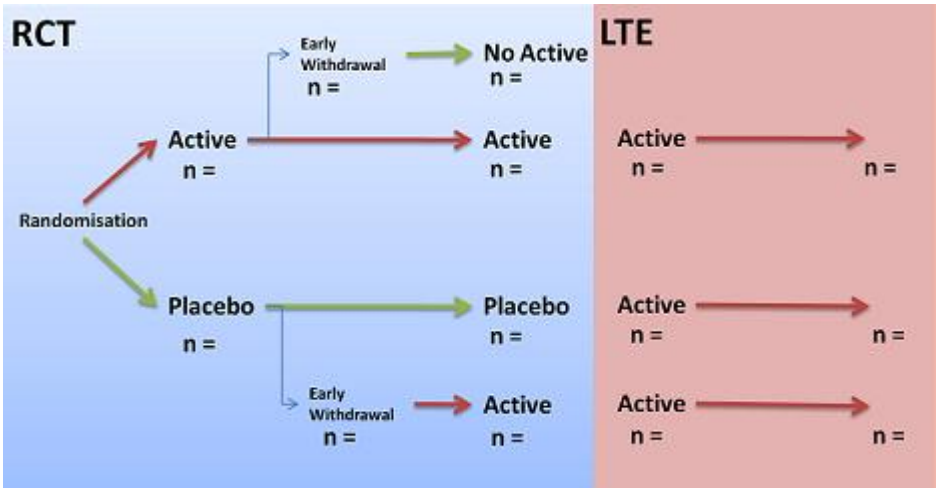
16. Regarding specific recommendations on the analysis of LTE studies, please rate your level of agreement to the statements below(0 = none to 10 = maximum) .

	0	1	2	3	4	5	6	7	8	9	10
The null hypothesis should be stated at the start	○	○	○	○	○	○	○	○	○	○	○
The null hypothesis must be related to the results achieved in the original RCT	○	○	○	○	○	○	○	○	○	○	○
Multiple comparisons should be taken into account when determining the level of statistical significance	○	○	○	○	○	○	○	○	○	○	○
The report should include details on how data for sustained effect was analysed	○	○	○	○	○	○	○	○	○	○	○
The plan for subjects that drop out of a LTE study should be specified	○	○	○	○	○	○	○	○	○	○	○
In a LTE study, the planned analysis of data to evaluate for sustained effect should be non-inferiority in nature	○	○	○	○	○	○	○	○	○	○	○
The analysis of the data from a LTE study 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.)	○	○	○	○	○	○	○	○	○	○	○
The analysis should include survival / retention rates	○	○	○	○	○	○	○	○	○	○	○
The analysis should include a pooled analysis from the original trial groups	○	○	○	○	○	○	○	○	○	○	○
An LTE study should preferably include hard endpoints (e.g. death, work disability, joint replacement surgery, hospital admission) from linkages with other data sources	○	○	○	○	○	○	○	○	○	○	○
The analysis of the data from a LTE study should take into account the dropouts	○	○	○	○	○	○	○	○	○	○	○

Please provide any additional comments/points that need to be considered related to the analysis and interpretation of LTE study data in the box below.

Reporting of LTE studies

Proposal of flow chart



Patients randomised to either group at the RCT may leave the trial early. Patients on the active arm may continue receiving the drug until the end of the RCT or discontinue it before ending. Patients on the placebo group may continue on placebo until the end of the RCT or start on the experimental drug before ending. At the start of the extension period two subgroups will be receiving the experimental drug and those in placebo may also commence active drug if they enter the LTE phase.

17. Please grade your level of agreement based on the flowchart above.

	0	1	2	3	4	5	6	7	8	9	10
All LTE reports must include a flow-chart on the progress of patients included	○	○	○	○	○	○	○	○	○	○	○
Grade your agreement with the flowchart above	○	○	○	○	○	○	○	○	○	○	○

Please provide additional comments on the flowchart in the space provided below:

18. Regarding specific recommendations on how to report the results of LTE studies, please rate your level of agreement (0 = none) to (10 = maximum) for the following statements:

(Some of these statements overlap with those made earlier, but we are now asking your opinion on what should always appear in the report)

	0	1	2	3	4	5	6	7	8	9	10
The taskforce should develop and detail minimal standards that should be included when reporting a LTE study by means of a checklist	○	○	○	○	○	○	○	○	○	○	○
The report of a LTE study should be consistent with and consolidate existing established guidelines including CONSORT and STROBE	○	○	○	○	○	○	○	○	○	○	○
The report of a LTE study should be consistent with the ACR/EULAR recommendations on the reporting of clinical trials in RA (Aletaha D, et al 2008)	○	○	○	○	○	○	○	○	○	○	○
A report of a LTE study should include a flow diagram detailing numbers at each relevant time-point	○	○	○	○	○	○	○	○	○	○	○
LTE studies should provide the same information for all randomised patients in terms of quantity and quality, irrespective of the nature of prior RCT	○	○	○	○	○	○	○	○	○	○	○
For those patients entering the LTE study having achieved LDA or remission during the RCT, the sustainability of such disease states should be evaluated and made available	○	○	○	○	○	○	○	○	○	○	○
For those subjects that enter a LTE study not having achieved remission/acceptable disease activity state following the RCT, the number that achieve this during the LTE study should be reported – to determine whether longer drug exposure has the potential to improve disease state of such subjects further	○	○	○	○	○	○	○	○	○	○	○
The drop-out rates from each arm during the original RCT and the cross-over groups should be available	○	○	○	○	○	○	○	○	○	○	○
All drop-outs should be detailed	○	○	○	○	○	○	○	○	○	○	○

Please provide any additional comments/points you believe may be relevant to the reporting of LTE

19. Regarding the nature and frequency of reports from LTE studies, please rate your level of agreement (0 = none) to (10 = maximum) for the following statements:

	0	1	2	3	4	5	6	7	8	9	10
The taskforce document should comment on the frequency of the reports of LTE studies	○	○	○	○	○	○	○	○	○	○	○
The taskforce document should comment on the nature of reports	○	○	○	○	○	○	○	○	○	○	○
The results of a LTE study should be reported every year	○	○	○	○	○	○	○	○	○	○	○
The results of a LTE study should be reported every two years	○	○	○	○	○	○	○	○	○	○	○
The results of a LTE study should be reported every three years	○	○	○	○	○	○	○	○	○	○	○
The results of a LTE study should be reported annually to a maximum of 5 years	○	○	○	○	○	○	○	○	○	○	○
The results of efficacy and safety of a LTE study should be reported together	○	○	○	○	○	○	○	○	○	○	○
Separate reports for efficacy and safety results of a LTE study should be written	○	○	○	○	○	○	○	○	○	○	○
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	○	○	○	○	○	○	○	○	○	○	○

Please provide any additional comments/points you believe may be relevant to the frequency or nature of LTE reports

Ethics

20. Regarding specific recommendations on the ethical issues involving LTE studies, please rate your level of agreement (0 = none) to (10 = maximum) for the following statements:

	0	1	2	3	4	5	6	7	8	9	10
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	○	○	○	○	○	○	○	○	○	○	○
The subjects included in a LTE study should sign a new informed consent form (different from the one for the RCT) for continuation of data collection	○	○	○	○	○	○	○	○	○	○	○
The subjects included in a LTE study should sign a new informed consent for continuation of drug	○	○	○	○	○	○	○	○	○	○	○
The subjects included in a LTE study should update consent each year	○	○	○	○	○	○	○	○	○	○	○

Do you foresee other ethical considerations that should be considered in the document?

21. And finally, are there any remaining issues you would like to raise?

Thank you very much for your input!

We promise that next surveys will be much much sorter!