Clinical considerations in determining a non-inferiority margin

Dear colleague,

You are invited to participate in a survey on "Clinical considerations in determining a non-inferiority margin".

This survey is part of a study to identify challenges in determining a non-inferiority margin using the case study of oral anticoagulants for prophylaxis of venous thromboembolic events (VTE) after orthopedic surgery. This survey forms part of a PhD-project. In a first part, we looked at statistical considerations when choosing a non-inferiority margin. In this part of the project, we aim to identify clinical considerations in choosing a non-inferiority (NI) margin and we would appreciate your participation in this survey.

The aim of the current study is to ask clinical and regulatory experts what they consider the appropriate NI margin for a future NI trial on oral anticoagulants, direct thrombin inhibitors (DTI) and direct XA inhibitors (DXAI), for prevention of VTE in patients undergoing elective hip or knee replacement surgery and what their motivations are to arrive at this NI margin.

Each participant will be asked to fill in the NI margin they find appropriate in a hypothetical scenario before and after additional information is given. In a second round, the results of the first round will be presented and again each participant will be asked to fill in their preferred NI margin.

We invite you to participate in this survey, because:

- You are a clinical expert in the field of anticoagulants, or
- You are an expert in the field of non-inferiority trials from a regulatory perspective, or
- You are a scientist from pharmaceutical industry on the topic of anticoagulants

This online questionnaire will take approximately 15 minutes of your time. This survey is for scientific purposes only. The information you provide will handled anonymously and kept confidential and will not be distributed to other people than those in the research group listed below.

This study is a PhD project and part of The Escher project: science-driven drug regulation and innovative research throughout phased drug development, from Top Institute Pharma (http://www.tipharma.com)

About us

We are a research group from the division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University and from the Julius Center, University Medical Center Utrecht, The Netherlands.
Best regards,
Grace Wangge, MD
PhD student

Other members of the research group are: Prof. A. de Boer, MD, PhD, Prof. A.W. Hoes, MD, PhD, O.H. Klungel, PharmD, PhD, M.J. Knol, PhD.

There are 18 questions in this survey

1. Your consent

Do you agree to participate in this study?

Please choose only one of the following:

- Yes
- No

Questions below only had been asked to people who agree to participate in the study

About you

First, we would like to know some information about you as an expert.

2. What is your age in years?

Please write your answer here:

3. Your gender:

Please choose only one of the following:

- Female
- Male
4. Your main profession (Please choose one):

- Regulator
- Clinician
- Researcher working in academia
- Researcher working in pharmaceutical industry
- Other (please specify):

5. Are you also a consultant for the pharmaceutical industry?

This question will only appeared if the answer was 'Regulator' or 'Clinician' or 'Researcher working in academia' at question '4' (Your main profession (Please choose one):

Please choose only one of the following:

- Yes
- No

6. Are you also a member of a regulatory agency (e.g. EMA, FDA)

This question will only appeared if the answer was 'Clinician' or 'Researcher working in academia' at question '4' (Your main profession (Please choose one):

Please choose only one of the following:

- Yes
- No

7. Were you ever involved in (the development of) any trial in either one of the topics below:

<table>
<thead>
<tr>
<th>Trials on the effect of anticoagulants</th>
<th>Yes</th>
<th>Uncertain</th>
<th>No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Trials on the effect of some intervention on the risk of venous thromboembolic events</th>
<th>Yes</th>
<th>Uncertain</th>
<th>No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Trials on patients undergoing any orthopaedic surgery</th>
<th>Yes</th>
<th>Uncertain</th>
<th>No</th>
</tr>
</thead>
</table>
8. Were you ever involved in (the design or conduct of) a non-inferiority trial?

Please choose only one of the following:

- Yes
- No

9. Were you ever involved in (the development of) a non-inferiority trial on one of the topics below:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>Uncertain</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials on the effect of anticoagulants</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials on the effect of some intervention on the risk of venous thromboembolic events</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials on patients undergoing any orthopaedic surgery</td>
<td>O</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. Were you ever involved in the evaluation of a protocol (e.g. as a member of an ethics committee or grant committee) or a manuscript (as a journal referee or editor) of a non-inferiority trial on one of the topics below:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>Uncertain</th>
<th>No</th>
</tr>
</thead>
<tbody>
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<td></td>
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<tr>
<td>Trials on the effect of some intervention on the risk of venous thromboembolic events</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials on patients undergoing any orthopaedic surgery</td>
<td>O</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Non-inferiority margin**

The aim of a non-inferiority (NI) trial is to show that a new treatment is not worse than its comparator, which typically is an active drug. NI trials can be used in a situation when a new drug considered has a similar efficacy profile as its comparator but may offer other advantages over the existing drug such as a novel method of administration or a better safety profile. In a regulatory setting, NI trials can be used to provide primary, but indirect, evidence of a new drug’s efficacy in cases where a placebo is not ethically justified.

The main step in designing an NI trial is pre-specifying an NI margin, i.e. a limit by which it can be established that the new drug is not worse than its comparator. An example is the SPORTIF
III trial (Lancet 2003;362:1691-98) that compared ximelagatran with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation. The NI margin in this trial was determined to be a risk difference of 2%. This means that an excess risk of 2% in the ximelagatran group as compared with the warfarin group was considered acceptable to declare that ximelagatran was not worse than warfarin. The trial showed that the risk of thromboembolism was xx% in the ximelagatran group and xx% in the warfarin group. Thus the risk difference is -0.7% and the 95% confidence interval -1.4 to 0.1%. The upper boundary of the confidence interval (0.1%) is below 2%, thus non-inferiority was concluded (see Figure).

In this example, the NI margin was defined based on a risk difference. An NI margin can also be defined on a relative risk scale, for example, the NI margin is a relative risk of 1.2.

Case study

As many of the trials in direct thrombin inhibitors (DTI) and direct XA inhibitors (DXAI) for prevention of VTE in patients undergoing elective hip or knee replacement surgery were NI trials, we use this as a case study to identify challenges in determining an NI margin.

Suppose that we would like to conduct an NI trial on a new and promising DXAI for prevention of VTE after orthopedic surgery. We will first provide some details on the proposed study. Then we will ask you to define an NI margin for this future trial. Next, we will provide more background information on previous studies in this field and ask you again to define an NI margin for the future trial.

Future trial

Suppose we want to conduct an NI trial on a new potent, selective, oral, DXAI, called escheraban, for prevention of VTE after orthopedic surgery. In previous phase II trials, escheraban has showed to be similarly safe and effective with enoxaparin.
The trial is a randomized, non-inferiority, double-blind, controlled trial in adult patients undergoing orthopedic surgery. Enoxaparin is used as the active comparator. The efficacy endpoint is the composite of established deep vein thrombosis, or pulmonary embolism (conformed by state-of-the-art imaging), or death from any cause during the intended treatment period (14 days). The primary safety outcome is bleeding during the treatment period or until 2 days after the last dose of study medication is administered. Treatment with escheraban will be started 12-24h after surgery.

Your opinion on NI margin in escheraban trial:

11. Which effect measurement would you choose for the escheraban trial?

- Risk difference (RD)
- Relative risk (RR)
- Both RD and RR
- Other (please mention): _________________

12. What excess risk of the composite efficacy endpoint in the escheraban group do you find acceptable to declare escheraban non-inferior to enoxaparin? (Please fill in the number below based on your choice of effect measurement above)

13. Please explain why you choose this specific NI margin. Provide your separate arguments briefly below:

Please write your answer here:

- __________________________________________________________________________
- __________________________________________________________________________
- __________________________________________________________________________
- __________________________________________________________________________
- __________________________________________________________________________

Background information

Most of the guidelines on NI trials only state that a margin should be based on both clinical and statistical considerations. However, a recently issued draft FDA guideline on NI trials (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf) includes a more specific guidance on how to determine an NI margin. The NI margin should be determined such that the new drug can be shown to be effective relative to placebo and needs to account for the uncertainty in the effect size of the active control versus placebo. To this aim the guideline introduced the concept of M1 and M2.

M1 resembles the most conservative effect of the active control compared with placebo, assumed present in the NI trial. The most conservative effect is defined as the upper bound of the
confidence interval of the (pooled) effect estimate of the difference between the active control and placebo. M1 is typically determined from earlier trials comparing the active control with placebo or a state-of-the-art meta-analysis of such trials. M2 reflects the clinical judgment about how much of M1 should be preserved to be the largest clinically acceptable difference (degree of inferiority) of the test drug compared to the active control. For example, if it were concluded that it would be necessary for a test drug to preserve at least 75% of an effect on a specific outcome, M2 would be 25% of M1, i.e. the loss of effect that must be ruled out. Determination of M2 provides (some) reassurance that the test drug will be superior to placebo and that the effect is clinically relevant.

We determined M1 and M2 for the future trial on escheraban following the steps of the draft FDA guideline.

**Determining M1**

First, we searched for placebo-controlled trials on enoxaparin, the active comparator in the future trial.

From Pubmed and Cochrane Central Register of Controlled Trials, we found six placebo controlled trials:

<table>
<thead>
<tr>
<th>Name of author</th>
<th>Date of publication</th>
<th>Duration of therapy (days)</th>
<th>Dosage of enoxaparin</th>
<th>Primary endpoint</th>
<th>Mean age of subjects</th>
<th>Female subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turpie, et.al</td>
<td>Oct-86</td>
<td>14</td>
<td>30 mg bid</td>
<td>DVT measured with venography</td>
<td>67</td>
<td>52</td>
</tr>
<tr>
<td>Leclerc, et.al</td>
<td>Jan-92</td>
<td>14</td>
<td>30 mg bid</td>
<td>DVT measured with venography</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>Kalodiki, et.al</td>
<td>Jun-96</td>
<td>8 - 12</td>
<td>40 mg qd</td>
<td>Composite of DVT measured with venography and PE</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Samama, et.al</td>
<td>Jan-97</td>
<td>10 ± 2</td>
<td>40 mg qd</td>
<td>Composite of DVT measured with venography and PE</td>
<td>69</td>
<td>42</td>
</tr>
<tr>
<td>Fuji, et.al (1)</td>
<td>Jun-08</td>
<td>14</td>
<td>20 mg qd, 20 mg bid, 40 mg qd</td>
<td>Composite of DVT measured with venography and PE</td>
<td>62</td>
<td>88</td>
</tr>
<tr>
<td>Fuji, et.al (2)</td>
<td>Jun-08</td>
<td>14</td>
<td>20 mg qd, 20 mg bid, 40 mg qd</td>
<td>Composite of DVT measured with venography and PE</td>
<td>70</td>
<td>84</td>
</tr>
</tbody>
</table>

Note: qd = quaque die (once daily), bid = bis in die (twice daily), DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venous thromboembolic events, RD = risk difference, RR = relative risk
Using the data of the placebo-controlled trials, we calculated a pooled risk difference and relative risk:

We decided to take the upper-bound of the 95% confidence interval of the pooled effect estimate based on the random effects model as M1. Thus, M1 based on a RD is -18% and M1 based on a RR is 0.64.
Determining M2

We calculated M2 by preserving 50% of the M1’s effect.

Based on this 50% preserved effect, M2 based on a RD is 9% (18% divided by 2).

The M2 based on a RR is 1.25. This is calculated based on the formula recommended by the draft FDA guideline:

\[
(1/M1)^{(1 \text{- preserved-effects})} = (1/0.64)^{(1 - 0.5)}
\]

14. Based on the new information, which effect measurement would you choose for the NI margin in escheraban trial?

- RD
- RR
- Both RD and RR
- Other (please mention): ____________________

15. What excess risk of the composite efficacy endpoint in the escheraban group do you find acceptable to declare escheraban non-inferior to enoxaparin? (Please fill in the number below based on your choice of effect measurement above)

16. Please explain why you choose this specific NI margin. Provide your separate arguments briefly below:

Please write your answer here:

- ____________________________________________
- ____________________________________________
- ____________________________________________
- ____________________________________________
- ____________________________________________

Thank you for your participation

17. If you have any colleague you would like to recommend to participate in this study, please list their name and email address below:

Please write your answer here:
18. If you have any comments or questions on this study, please put them below:

Please write your answer here:

**Questions below only appeared for people who refused to participate in this study**

You refused to participate in this study

2. Please, give the reason why you do not want to participate in this study

Please write your answer here:

3. Can you suggest a colleague that would be interested to participate in this survey? (please provide name and email address)

Please write your answer here:

This is the end of the survey

Thank you for your contribution

Submit your survey.
Thank you for completing this survey.