Trial Steering Committee (TSC) Charter

Tapering of rituximab based on interval prolongation compared to disease activity-guided dose reduction in patients with rheumatoid arthritis: the RITUXERA trial

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Clinicaltrials.gov NCT06003283

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1. Introduction

This Trial Steering Committee (TSC) Charter is for the trial entitled "*Tapering of rituximab based on interval prolongation compared to disease activity-guided dose reduction in patients with rheumatoid arthritis: the RITUXERA TRIAL*" for which UZ Leuven is Sponsor and Prof. Dr. Patrick Verschueren is the Coordinating Investigator for the trial.

Trial objectives are described in the research protocol. The purpose of this document is to establish a TSC, describe the role and responsibilities of the TSC, including the timing of meetings, methods of providing information to and from the TSC, frequency and format of meetings, statistical issues and relationships with other committees (if any) or stakeholders.

The charter is intended to be a living document. The TSC shall regularly review the charter to determine whether any changes are needed.

2. Responsibilities of the TSC

The TSC is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The TSC is required to provide recommendations about (re-)starting, continuing, and terminating the study.

The timing of TSC-reviews is described in each individual protocol. In addition, ad hoc reviews will be undertaken if there are specific safety concerns. The study will not stop enrolment awaiting these TSC reviews, however the TSC may recommend temporary or permanent cessation of enrolment based on its safety reviews.

The TSC interim monitoring may result in early termination of the trial for reasons of futility, inefficacy, or safety.

The Project Manager (PM) and/or Trial Data Manager (DM) will provide necessary data reports to the TSC to allow the TSC to review trial progress and assess, in particular:

- Selection, recruitment retention of participants
- Organization, quality and implementation of trial protocol and data collected
- Evidence for treatment differences in the main efficacy outcome measures
- Evidence for treatment harm (e.g., toxicity data, SAEs, deaths, other adverse event and/or safety data)
- Monitor compliance with the protocol by investigators and participants
- Assess compliance with previous TSC recommendations

Based on the above and with consideration for any ethical implications, the TSC will make recommendations, as appropriate about:

- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs
- Participant safety

- Notification of and referral for abnormal findings
- Trial continuation or termination of the trial for everyone, for some treatment groups and/or for specific participant subgroups
- Modifications to the protocol, eligibility criteria, trial endpoints, sample size etc.
- Additional data analyses.

The TSC members' acceptance of each final version of the TSC charter content and the roles and responsibilities of TSC members laid out in the charter will be documented in the meeting minutes pertaining to the first TSC meeting that occurs following any revisions to the charter.

3. TSC members and interactions

TSC members are selected for their relevant expertise with regards to the disease pathology and/or data analysis. The TSC will have a Chair.

The PM and/or DM will prepare each TSC meeting by gathering input from the Sponsor and/or the Ethics Committee on particular topics of concern. For each meeting, the PM and/or DM will prepare summary reports and tables to facilitate the oversight role of the TSC. The TSC should discuss at the first or subsequent meetings what data they wish to review and how it should be presented.

4. Scheduling, Timing and Organization of Meetings, Voting procedure

TSC meetings are usually held by remote connections and will take place 3 times per year.

The purpose of the TSC's **first meeting** is to review and discuss this Charter, to consider the protocol(s) in detail, provide an overview of study activities, to review and make recommendations about the protocol(s) how the TSC might respond to hypothetical situations. During this first meeting TSC members will formally review and accept the TSC charter, hence confirming (1) that they agree to be a member of the TSC and (2) that they agree with the contents of this Charter. If a potential TSC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these during the first meeting and may decide not to accept the invitation to join. The TSC members will be asked if they have any conflicts of interest.

After the first meeting which should take place as soon as possible and preferably before the start of the study, meetings are held as specified in the trial protocol, with additional meetings or conference calls scheduled **as needed**. In any event, the TSC should meet within one year of recruitment start.

The agenda for TSC meetings and calls will be drafted by the PM and/or DM. They will finalize the agenda after consultation with the TSC Chair. The agenda and meeting materials should be distributed to TSC members at least one (1) business day in advance of each TSC meeting or call.

During the **final session**, the TSC Chairperson will verbally communicate the final TSC recommendation directly to representatives of the Sponsor and/or the Ethics Committee, as applicable along with any safety concerns the TSC may have.

Before each meeting, when the agenda is sent out, TSC members will be asked to state whether they have developed any new conflicts of interest since the previous TSC meeting. If a new conflict is reported, the Chair and other members will determine if the conflict limits the ability of the TSC member to participate in the discussion, and whether further evaluation of the conflict by the UZ Leuven Ethics Committee "Research", may be warranted.

It is expected that all TSC members will **attend** every meeting and call. However, it is recognized that this may not always be possible. At least half of the members, including the Chair, must be present in order to let the meeting take place. If the TSC is considering recommending major action after a meeting without all members being present, the TSC Chair should talk with the absent members as soon after the meeting as possible to check if they agree. If they do not, a further teleconference should be arranged with the full TSC. If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the TSC. If a member does not attend a third meeting, they should be replaced.

After review and discussion of each Data Report, the TSC members will vote to determine the final TSC recommendation within one of the following options:

- Continue the study without modification
- Continue the study and amend the protocol, as specified
- Pause enrolment, pending resolution of a specified issue or concern
- Suspend further enrollment in the trial pending analysis of events and/or data
- Terminate recruitment in a subgroup of patients
- Terminate a specific treatment arm
- Terminate the study

As part of the recommendations, the TSC may also make comments and suggestions that might enhance study performance, as deemed appropriate.

Quorum for **voting** is considered to be half the number of standing members plus one. In case of a tie, the TSC Chair holds the deciding vote. All standing TSC members are voting members. The TSC has to decide in advance whether *ad hoc* members, invited for their expertise on specific topics, can vote.

The TSC Chair will provide a formal, written communication of the TSC recommendation in the form of a TSC recommendation letter. The TSC recommendation letters should be written by the TSC Chair and should be provided to Prof. Dr. Patrick Verschueren (the coordinating investigator) and all Principal investigators of the trial within 1 business day after the TSC recommendation is finalized.

Communications of the TSC recommendations will reflect the final recommendation of the TSC members. In the event that a unanimous decision cannot be reached, majority and dissenting opinions will be summarized and presented by the TSC Chair.

5. Implementation of TSC recommendations

The recommendations provided to the Sponsor by the TSC should be treated as such. The ultimate responsibility to implement or take action based upon the recommendations of the TSC will be made by the Coordinating Investigator.

The Coordinating Investigator for the study will notify the TSC Chair in writing of actions taken in response to a given TSC recommendation, for cases in which Sponsor action other than to continue the study without modification was recommended.

6. Confidentiality of TSC meetings

All members of the TSC shall keep confidential information that is being discussed during the meetings. TSC members are only allowed to discuss issues from their involvement in the trial(s), twelve (12) months after the primary trial results have been published, or when permission is agreed with the TSC Chair and UZ Leuven Clinical Operations Director.

7. Reports of TSC deliberations

- TSC meeting minutes will reflect attendance, as well as whether each individual attended in person or via teleconference.
- The PM and/or DM will produce minutes of all sessions of TSC meetings.
- Draft minutes will be provided to the TSC Chair for review and approval, before wider distribution.
- Once approved by the TSC Chair, the PM and/or DM will distribute the final minutes to all attendees within two (2) business days.
- Following each TSC meeting, the Chair will provide the TSC recommendation letter to the Coordinating Investigator and all Principal Investigators.
- The PM and/or DM will archive the final minutes. After database lock, the PM and/or DM will provide all minutes to the Sponsor for filing in the Trial Master File (TMF).

8. Statistical monitoring guidelines

At the first TSC meeting, review of the protocol will include review of the statistical analysis plan (SAP) and criteria for assessing futility, inefficacy and safety. The TSC should discuss the adequacy of the SAP and the statistical monitoring procedures proposed to guide its recommendations about termination, hold, continuation or restarting of the trial. These procedures could include guidelines for early termination for lack of benefit, termination for futility, and termination for safety reasons.

9. After the trial

At the end of the trial, there may be a meeting to allow the TSC to discuss the final data and give advice about data interpretation.
The proposed publication shall be presented for review and comment to the TSC prior to submission for publication.

10. Record retention

The PM and/or DM will file all TSC meeting minutes and any materials, reports etc. reviewed during the TSC meetings, in a restricted access folder until end of trial has been formally notified to the Ethics Committee and/or Competent Authorities (as applicable), after which all documentation of TSC operations are transferred to the Trial Master File for long term archiving in accordance with applicable regulations.

11. Version history

Version	Reason for change
1.0_20240125	New document

12. Signature

Name and surname:
Date:

Appendix A - TSC members and their expertise

UZ Leuven Ethics Comité "Research": Prof. Dr. Minne Casteels (EC President)
[redacted]

TSC members	Function	Contact Details
Prof. Dr. Kurt De Vlam	Chair	[redacted]
Prof. Dr. Patrick Verschueren	Coordinating Investigator	[redacted]
Prof. Dr. Daniël Blockmans	Expert	[redacted]
Marc Thelissen	Patient expert	[redacted]
Johan Joly	Project Manager	[redacted]
Dr. Elias De Meyst	Data Manager	[redacted]

Appendix B – Template Letter with TSC recommendation

This letter is sent to the Coordinating Investigator and Principal Investigators by the TSC Chair after each meeting, outlining the determinations of the TSC and giving reasons for any suggestions and/or modifications to the study plan or enrollment.

TSC Report and Recommendations

Study: Tapering of rituximab based on interval prolongation compared to disease activity-guided dose reduction in patients with rheumatoid arthritis: the RITUXERA TRIAL

To: Coordinating/Principal Investigator

Meeting Date:

Attendees: [List TSC voting members present]

Recommendations:
☐ Continue the study without modification
☐ Continue the study and amend the protocol, as specified
☐ Pause enrolment, pending resolution of a specified issue or concern
☐ Suspend further enrollment in the trial pending analysis of events and/or data
☐ Terminate recruitment in a subgroup of patients
☐ Terminate a specific treatment arm
☐ Terminate the study
☐ Other (see Comments)

Comments:

[Specific comments from the meeting. Rationale for making suggestions and modifications.]

Name and Signature of Chair:

Date:

Appendix C – Template TSC Meeting Minutes

Meeting date: DDMMYYYY

Meeting minutes date: DDMMMYYYY

TSC Member	Initials	Presence	Conflict of intrest	Comments
Prof. Dr. Kurt De Vlam	KDV	☐	☐	
Prof. Dr. Patrick Verschueren	PV	☐	☐	
Prof. Dr. Daniël Blockmans	DB	☐	☐	
Marc Thelissen	MT	☐	☐	
Johan Joly	JJ	☐	☐	
Dr. Elias De Meyst	EDM	☐	☐	

Quorum met? <if applicable, indicate: Yes or No>

Confidentiality

The TSC members understand and acknowledge to respect the confidential nature of the TSC-meeting.

Agenda

<insert>

Conclusion

<insert>

TSC recommendations **<check one, as applicable>**

- ☐ Continue the study without modification
- ☐ Continue the study and amend the protocol, as specified
- ☐ Pause enrolment, pending resolution of a specified issue or concern
- ☐ Suspend further enrollment in the trial pending analysis of events and/or data
- ☐ Terminate recruitment in a subgroup of patients
- ☐ Terminate a specific treatment arm
- ☐ Terminate the study
- ☐ Other (see Comments)

<insert additional comments>

Action items

<insert>

Next TSC meeting

<insert>

Required data for next TSC meeting

<insert>