A randomised trial of non-selective versus selective adjuvant therapy in high risk apparent stage 1 endometrial cancer

DGOG Group Specific Appendix

Overview of trial organisation

This trial has been initiated by the University College London (UCL). Within the Netherlands the University Medical Center Groningen (UMCG) is the "Country Coordinating Centre", representing all participating Dutch Gynecologic Oncology Group (DGOG) clinical sites ("DGOG clinical sites"). The protocol was designed by the Trial Management Group and will be followed in all DGOG clinical sites.

This document provides additional information about trial conduct specifically in the Netherlands and **therefore it supersedes the corresponding chapters in the protocol**.

- The Cancer Research UK and UCL Trials Centre (UCL CTC), 90 Tottenham Court Road, London, W1T 4TJ, is the coordinating data centre in this trial and they are responsible for the overall trial conduct (including protocol finalisation, trial activation, central data management, statistical analysis and publication).
- This DGOG Specific Appendix details the participation of all Dutch clinical sites and **therefore it supersedes the corresponding chapters in the protocol**.
- Within the Netherlands local trial coordination, data management and central and on-site monitoring will be performed by the Netherlands Comprehensive Cancer Organisation (IKNL).

Title page

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Funding in the Netherlands	Dutch Cancer Society grant RUG 2014-7433
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Principal Investigator for sentinel node sub study in the Netherlands	Dr. Ronald P. Zweemer
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Section 3 Trial Design

The Country Coordinating Centre (UMCG) will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial in the Netherlands:

- Approval from the Medical Ethical Committee in the UMCG (UMCG-METc)
- Adequate funding for trial coordination in the Netherlands

Section 4 Selection of Sites/Site Investigators

Before a site is activated, the Country Coordinating Centre (UMCG) will arrange a site initiation with the site which the PI and site research team must attend. Site initiation will either be performed for each site by teleconference, or as part of a pre-planned (national) trial launch meeting.

The Country Coordinating Centre (UMCG) will request activation of DGOG clinical sites by the UCL CTC once the following documents have been obtained:

- CV of local principal investigator, including proof of GCP training
- All relevant local approvals
- Signed clinical trial agreement between the DGOG clinical site and Country Coordinating Centre

Section 5 Informed Consent

It is the responsibility of the local investigator to ensure that this study and the procedures to obtain informed consent are conducted in compliance with all relevant Dutch regulations as well as the local governance and institutional policies. Informed consent forms of Dutch patients will be stored in the investigator site file of the hospital that enters the patient into the trial. Patients will have a minimum of 3 days to consider and discuss participation in the trial.

Section 6 Selection of Patients

Pre-randomisation reviewing of the diagnostic histological specimen, or hysterectomy and BSO specimen if randomisation is occurring after surgery, will preferably be performed by a specialised gynaecological oncology pathologist. In the absence of a specialised gynaecological oncology pathologist, samples may be assessed by a pathologist with ample experience in assessing gynaecological samples.

No blood samples will be taken for translational research in the Netherlands.

Section 7 Randomisation Procedures

Year of birth will be the only patient-identifier needed to perform the randomisation procedure. Furthermore, inclusion and exclusion criteria and site name, baseline assessments, stratification data, details of informed consent and confirmation that baseline QoL has been completed must be entered onto the online randomisation server hosted by UCL CTC. Please note: baseline assessments may only be performed after informed consent has been signed.

For queries concerning randomisation of patients please email UCL CTC and copy in the Country Co-ordinating Centre (UMCG) using the contact details below.

a) UCL CTC email: ctc.statec@ucl.ac.uk
b) UMCG email: STATEC@og.umcg.nl

A randomisation manual will be provided with additional instructions.

Section 8 Trial Treatment

Before patients may be entered into the sentinel node sub-study they must receive the sentinel lymph node patient information file. Furthermore, specific written informed consent for this sub-study must be provided.

Surgical specimens will preferably be assessed by a specialised gynaecological oncology pathologist. In the absence of a specialised gynaecological oncology pathologist, samples may be assessed by a pathologist with ample experience in assessing gynaecological samples.

As STATEC is primarily a surgical trial, the protocol does not mandate a specific adjuvant therapeutic regime (chemotherapy and/or radiotherapy). The protocol provides a number of options to choose from.

Additional information regarding adjuvant therapy may be found the Adjuvant treatment guidance document, supplied by UCL CTC, which is applicable for all centres participating in the STATEC trial.

Section 9: Assessments during follow-up

Quality of life questionnaires have been saved as ‘version A’, ‘version B’ and ‘version C’. The tables below show which version should be distributed at which timepoint.

Quality of life questionnaire version A includes:

- EORTC QLQ-C30
- EORTC QLQ-EN24
- EORTC QLQ-OV28 (items 52-54)
- EORTC QLQ-CX24 (items 41, 43, 44)
- EORTC QLQ-PR25 (items 39-40)
- Self-report lower extremity lymphoedema screening questionnaire
- Health Economics questionnaire (EQ-5D-5L)

Quality of life Questionnaire version B includes:

- EORTC QLQ-C30
- Health Economics questionnaire (EQ-5D-5L)

Quality of life Questionnaire version C includes:

- EORTC QLQ-C30
- EORTC QLQ-EN24
- EORTC QLQ-OV28 (items 52-54)
- EORTC QLQ-CX24 (items 41, 43, 44)
- EORTC QLQ-PR25 (items 39-40)
- Health Economics questionnaire (EQ-5D-5L)

Table 1 Group 1A and 1B patients: Quality of Life questionnaires

Time point														
Investigation	**3-5 weeks after surgery**	**3 weeks after starting adjuvant treatment**	**End of all adjuvant treatment**	**Year 1, 3 monthly** **First visit defined in section 9.3**				**Year 2** **4 monthly**			**Year 3** **6 monthly**		**Year 4 & 5** **Annually**	
				Months				**Months**			**Months**		**Months**	
				3	**6**	**9**	**12**	**16**	**20**	**24**	**30**	**36**	**48**	**60**
QoL-Questionnaires Version A	X					X	X	X		X		X	X	X
QoL-Questionnaires Version B		X (node + only)			X (node – only)									
QoL-Questionnaires Version C			X											

Table 2 Group 2A and 2B patients: Follow Up Assessments

Time point														
Investigation	**3-5 weeks after surgery**	**3 weeks after starting adjuvant treatment**	**End of all adjuvant treatment**	**Year 1, 3 monthly First visit defined in section 9.3**				**Year 2 4 monthly**			**Year 3 6 monthly**		**Year 4 & 5 Annually**	
				Months				**Months**			**Months**		**Months**	
				3	**6**	**9**	**12**	**16**	**20**	**24**	**30**	**36**	**48**	**60**
QoL- Questionnaires Version A	X					X	X	X		X		X	X	X
QoL- Questionnaires Version B		X												
QoL- Questionnaires Version C			X											

Section 10 Translational Research

No blood samples will be taken for translational purposes. Moreover, the retrospective central pathology QA is not applicable for the Dutch participants.

Please refer to the Biospecimen Sampling Manual for instructions for storage and transport of tissue from Dutch patients for translational research. All samples should be labelled with the patient trial ID and date of sample collection.

Section 11 Data Management and Data Handling Guidelines

Data entry will be conducted by data managers from IKNL. All IKNL-employees have signed a confidentiality agreement. After randomisation has been completed, the randomisation eCRF must be completed ASAP, all other relevant eCRF forms must be completed within 28 days of the patient being seen. UCL CTC will regularly report actual timelines for eCRF completion to allow IKNL to check whether the deadline of 28 days is being met.

The IKNL data managers will be responsible for processing data queries from UCL CTC. For data correspondence, send to:

IKNL Data Manager email: trialbureau@iknl.nl
Cc UMCG email: STATEC@og.umcg.nl

Section 12 Safety Reporting

The SAE reporting process is as follows:

1. Sites complete the initial trial specific SAE form to email to UCL CTC within 24 hours of becoming aware of the SAE. Please note that this is not part of the eCRF/database, and will be provided before sites are opened.
    a. Ensure all sections available in the SAE form are completed for the initial report.
    b. Ensure that the patient's trial number is written down on all documentation.
    c. Ensure that participant identifiers are removed/blacked out on any supporting documentation to maintain confidentiality.
    d. If the event is not being reported within 24 hours of becoming aware of the SAE, please outline the circumstances that led to the delay in the SAE report to avoid unnecessary queries.
2. Complete SAE cover sheet.
3. Scan the SAE cover sheet + SAE form and email to UCL CTC and cc to UMCG
    a. UCL CTC: ctc.statec@ucl.ac.uk
    b. UMCG: STATEC@og.umcg.nl
4. When the SAE form is received, UCL CTC will send an SAE email receipt to the relevant DGOG clinical site and cc UMCG.
5. If the reported SAE is indeed assessed as a related unexpected serious adverse reaction (RUSAR) by UCL CTC, UCL CTC will contact the Country Coordinating Centre (UMCG). The

Country Coordinating Centre (UMCG) will then report the SAE through the web portal *ToetsingOnline* to the UMCG-METc, within 7 days for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other related SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

6. All RUSARs will be followed up until resolution. The site investigator must provide follow up information to the initial SAE reports if the RUSAR has not resolved at the time the initial report was submitted.

IKNL data managers may receive queries concerning SAEs from UCL CTC. The IKNL data managers will work together with the investigators from the DGOG clinical sites to resolve the queries. Any data provided must have the patient's trial number and year of birth clearly indicated, and any other patient identifiers must be removed/blacked out to maintain confidentiality in accordance with data protection laws in the United Kingdom and the Netherlands. For SAE query correspondence, send to:

IKNL Data Manager email: trialbureau@iknl.nl
Cc UMCG: STATEC@og.umcg.nl

UCL CTC will be responsible for determining whether an SAE is related or unrelated. Unrelated serious adverse reactions do not need to be reported to the UMCG-METc. RUSARs from international (non-DGOG) clinical sites will be discussed within the STATEC Trial Management Group and will be reported to the UMCG-METc in the STATEC annual progress/safety report. This will be sent on an annual basis to the Country Coordinating Centre (UMCG) for forwarding to the UMCG-METc.

Section 14, Trial monitoring and oversight

Please refer to protocol section 14.1 for guidance on central monitoring and to the Investigator Site File for details of the STATEC Monitoring Plan. Central and on-site monitoring of DGOG clinical sites will be conducted by monitors from IKNL. DGOG clinical sites must arrange access to (electronic) files of patients participating in the study for registrars and monitors from IKNL. For monitoring purposes, UCL will send IKNL a request for the collection of central monitoring documentation from all DGOG clinical sites every two years. IKNL will forward these monitoring requests to DGOG clinical sites for completion. IKNL will collect all requested documentation, check for completion and forward to UCL.

Should any issues arise from the central monitoring requests provided by UCL CTC, UMCG will be responsible for liaising with sites in the Netherlands until resolution.

Monitoring will follow ICH-GCP guidelines, with intensity of monitoring based on guidelines from the Netherlands Federation of University Medical Centres (NFU).

IKNL monitor email: monitor@iknl.nl

The informed consent forms will be filed in the Investigator Site Files at the DGOG clinical sites, no copies of these forms will be submitted to the Country Coordinating Centre (UMCG) or UCL CTC.

Section 16, Trial closure

According to Dutch law, DGOG clinical sites must retain and preserve all study materials for 15 years from study completion. Study materials include, but are not limited to, (copies of) signed informed consent forms, protocol, correspondence and investigator site files.

Section 18, Ethical approvals

The responsible investigator at DGOG clinical sites will ensure that the trial is conducted in compliance with the protocol and any amendments, as well as all relevant Dutch laws as detailed in the Clinical Trial Agreement. The study will be conducted according to the principles of good clinical practise.

The Country Coordinating Centre (UMCG) will submit a summary of the progress of the trial to the UMCG-METc once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, number of RUSARs, other problems, and amendments.

Amendments are changes made to the study after a favourable opinion by the accredited METc has been given. All amendments will be notified by the Country Coordinating Centre (UMCG) to the UMCG-METc.

Section 19, Sponsorship and indemnity

The UMCG is the local sponsor and the legal entity responsible for the conduct of the trial in the Netherlands. In accordance with Dutch law, the UMCG holds insurance against claims from participants for injury caused by their participation in this clinical trial.

Indemnity arrangements for the DGOG clinical sites are set out in the Clinical Trial Agreements between the DGOG clinical sites and the Country Coordinating Centre (UMCG). Liability insurance for the clinical sites is covered by the individual participating hospitals. A copy of the liability insurance form of the participating centre must be submitted by the site to the Country Coordinating Centre (UMCG) if requested.

Section 20, Funding

The Dutch Cancer Society is financially supporting the execution of the trial in the Netherlands.

Appendix 2: Quality of life substudy

Quality of life questionnaires will be distributed by the study personnel at the DGOG clinical sites at baseline, 3-5 weeks after surgery, 3 weeks after starting adjuvant treatment and at the end of all adjuvant treatment. IKNL will remind the DGOG clinical sites of these time points.

At baseline, patients will complete a form allowing IKNL to send quality of life questionnaires to their home address. This form, containing the home address of the patient, will be sent to IKNL. IKNL will be responsible for distribution of quality of life questionnaires at all remaining follow-up time points. IKNL will mail the paper-based questionnaires to the home address provided by the patient. Patients will be asked to complete the paper-based questionnaires, and return them to the respective DGOG clinical site using the enclosed labelled envelope. Personnel at the DGOG clinical site will scan and email the completed questionnaires to UCL CTC.

Appendix 3: Sentinel lymph node sub-study

Sentinel lymph nodes will preferably be assessed by a specialised gynaecological oncology pathologist. In the absence of a specialised gynaecological oncology pathologist, samples may be assessed by a pathologist with ample experience in assessing gynaecological samples