PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The IDEAL DVT study, individualized duration elastic compression therapy against long-term duration of therapy for the prevention of post thrombotic syndrome, a randomized controlled trial
AUTHORS	ten Cate, Arina; Bouman, Annemieke ; Joore, Manuela; Prins, Martin; ten Cate, Hugo

VERSION 1 - REVIEW

REVIEWER	Mark H.H. Kramer Professor of Internal Medicine VU University Medical Centre Amsterdam The Netherlands
REVIEW RETURNED	20-Apr-2014

GENERAL COMMENTS	Post thrombotic syndrome can be a debilitating complication of deep venous thrombosis of the leg. Elastic compression therapy (ECT) is not easy to comply with. This study tries to investigate the possibility of individualizing this therapy. The study is well designed and appropriately powered.

REVIEWER	Hugo Partsch Emeritus Professor of Dermatology Medical University of Vienna Austria
REVIEW RETURNED	21-Apr-2014

GENERAL COMMENTS	This is an excellent study concept which will provide important information about the value of individually tailored compression therapy after DVT to prevent PTS. 1. My main point of concern relates to the 6 weeks long inclusion period after the acute stage of DVT in which either no compression, compression by bandages or by stockings may be applied. These open treatment options for such a long time period may influence the outcome considerably. The initial management of DVT plays a deciding role for the inflammatory process involving the vein walls and the progression /regression of the clot, both of which are the basis for the development of PTS. In order to avoid such confounding variables the study should start as early as possible after the acute event. The details of the conservative management of acute DVT including the strategy of anticoagulation, compression and mobilization needs to be standardized. A uniform protocol for the management of DVT among the centers is highly recommended.

	2. Assessments at any time point, including the first visit, should include the CEAP classification, at least concentrating on clinical signs (C). Both, Villalta scale and CEAP are non-specific for PTS and the assessment of changes should also include the initial stage at entry. 3. Outcomes: change of CEAP should be added as a secondary outcome (occurrence of skin changes!) and should also be checked at each follow up. 4. Additional objective parameters would be helpful. It would be easy to measure the circumference of both legs at predefined points in order to characterize leg swelling. 5. VAS or modified Lowenberg test to quantify pain should be considered. 6. Basic Duplex data, at least followed every 12 months, would increase the scientific image of the study. It may be assumed that patients with initial reflux will have a higher risk of developing pathological Villata values in the following years, even when no clinical signs like varicose veins are present initially. 7. Since the compliance of wearing the stockings is a major issue a diary given to the patients could be considered. 8. Some professional instruction for the patients how to apply and handle the stockings would improve compliance. 9. Stocking length and time of renewal need to be defined. 10. Since the dosage of compression is an essential part of therapy it would be advisable to measure the stocking -pressure at predefined points at least in a subgroup of patients (after application of a new stocking and before this is replaced by a new one). 11. Since different brands of compression stockings have different elastic properties which may influence the outcome in addition to the resting pressure alone, it would be advisable that all centers use the same product. 12. Contraindication: intermittent claudication is a rather vague point, especially in DVT-patients who may have walking problems due to their underlying disease. Should be replaced by measurement of ABPI, e.g. excluding patients with an ABPI< 0.8. 13. The three scenarios described do not take into account that there might be also a worsening after initial improvement, in accordance with the concept of a “latency period”. Would such a case stay untreated up to two years?

REVIEWER	Susan Kahn McGill University, Montreal, Canada
REVIEW RETURNED	22-Apr-2014

GENERAL COMMENTS	This manuscript describes a clinical trial protocol of the IDEAL study, an RCT of individualized duration elastic compression therapy vs. long term duration elastic compression stockings (ECS) therapy for prevention of post-thrombotic syndrome. The role of ECS in both PTS prevention and treatment is as yet unclear, particularly in light of a recently published multicentre placebo-controlled RCT suggesting that ECS are not of benefit to prevent PTS, hence this is a clinically relevant study. Critique/suggestions:

	Title: change ‘against’ to ‘versus’ Abstract: Last line of Methods and analysis: change ‘after’ 24 months to ‘at’ 24 months Under Ethics and dissemination: unclear what “broad application” means- clarify. It is unusual to have a subheading “Ethics and dissemination” in a manuscript abstract. Could change to Clinical relevance Manuscript: Background: I found the background section to be disorganized and the argument building up to the need for the IDEAL Trial was not as clear as it could be. What is the overall specific aim of the IDEAL trial? What are the primary and secondary objectives, and why? Give number of patients studied in “our management study” (p3 line 47). What were the limitations of the management study such that a multicentre trial was needed? What type of currency is being described on p 4 line 8 and 9 (ie dollars? Euros?) Unclear if p4 lines 25-30 refer to the IDEAL trial (re: we will perform…). Avoid use of “broad” application- this is not correct English. Methods/design: Change “fair” to balanced. (p4 line 54). It is not well explained why you are stratifying for age sex and BMI. Also, BMI is a continuous variable- thus, how do you stratify for BMI? Are you using BMI ‘bands’? If yes, bands of what width? P5 line 4: It is stated that the primary outcome is PTS at 24 months after DVT, but from the analysis it appears to be PTS within 24

	months of DVT – clarify P5 line 26: are patients being included within 6 weeks after DVT? A critique of some previous ECS trials is that the ECS were not applied quickly enough- 6 weeks seems like a long time-justify. In fact, need to make it more clear throughout paper what is the timepoint of inclusion/randomization- at DVT diagnosis? After 6 months of use of ECS? P6 line 26: If you exclude patients who develop recurrent DVT within 6 months follow-up, this is post randomization exclusion and contravenes the ITT analysis principle- need to justify. Why do you exclude patients with pre-existing CVI- these may be patients most likely to benefit from stockings. I suggest for the readers' sake that you provide a brief rationale for all the exclusion criteria. Page 6 line 14: Is it considered ethically acceptable for the coordinating centre in Maastricht to contact patients directly to inform them of their allocation group? Do patients provide consent for this, specifically? In North America it would not be allowed for someone outside the patient's treating centre to be given patient identifying information and to directly contact the patient. P6 line 51: "Once stopped, ECS will not be reinstated"-what if a patient develops symptoms of PTS? How can one justify not reinstating ECS to control symptoms if PTS develops? P. 7 line 41. What is the hypothesis concerning the patient preferences DCE substudy? How many patients will receive the DCE questionnaire, and how will data be analysed/interpreted. If the trial's main result shows lack of non-inferiority of individually tailored ECS but patients prefer not to wear ECS based on DCE substudy, how will the overall results be interpreted? Suggest providing more details on the rationale for and interpretation of this interesting substudy. P8 line 7: Crossover sentence is unclear- in what situations might crossover occur? If patients whose ECS were discontinued early (in experimental arm) later develop symptomatic PTS, wouldn't there be an obligation to instate ECS for symptom control? Will such "off label" ECS use be systematically tracked and reported?

	What is the hypothesis with regard to the cost utility analysis? Sample size calculation- it is unclear if the 7.5% difference represents the upper bound of the confidence interval of difference in rates of PTS between groups, or rather the point estimate. If the latter, what is the upper bound of the CI? Unclear what is meant by "this proportion of loss in efficacy is customarily accepted…."-clarify and provide a reference. A 2% rate of loss to follow in a trial of 2 years duration seems overly optimistic, especially as patients with cancer are not explicitly excluded from participating. Can the authors provide justification based on previous similar trials (with supporting references)? If 2 consecutive + Villalta scores are required to diagnosis PTS, in the time to event analysis, which timepoint will be attributed as the timepoint of PTS development- the first, or the second? This should be stated. The analysis section requires more details- how will the QOL and DCE data be analysed? The ANOVA sentence is quite vague. Why adjust for age and sex (both are stratification variables) but not BMI (also a stratification variable). Will you adjust for centre-this is also a stratification variable, as per Methods. How will the results be interpreted? If there are no differences between groups in the 2-year cumulative incidence of PTS, how will you be able to determine that this is because individually tailored ECS are as effective (ie non-inferior) to 2 years of ECS- it could also be interpreted that ECS, whether individually tailored or worn for 2 years, equally do not influence the risk of PTS- ie no effect of either intervention. As all patients receive ECS (for varying durations), if individually tailored ECS are as effective (ie non-inferior) to 2 years of ECS, couldn't the explanation be that ECS palliated symptoms of PTS in patients who were destined to develop PTS, and were not needed in patients who didn't develop PTS? That is, how will you distinguish whether ECS prevented PTS versus palliated symptoms of existing PTS, in those patients who developed PTS? Ethical considerations: please indicate if the participating centres ethics committees (both in Italy and the Netherlands) approved the study, not just the coordinating centre's ethic committee.

	The SOX Trial is criticized for imperfect compliance- it would be more balanced to add that a per protocol analysis of frequent ECS users was consistent with the main analysis in showing no effect of ECS. Last sentence: when is the study expected to complete recruitment, and thus when are results expected? This information would be helpful to the reader.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Mark H.H. Kramer
Institution and Country Professor of Internal Medicine
VU University Medical Centre
Amsterdam
The Netherlands
Please state any competing interests or state 'None declared': None declared

Post thrombotic syndrome can be a debilitating complication of deep venous thrombosis of the leg. Elastic compression therapy (ECT) is not easy to comply with. This study tries to investigate the possibility of individualizing this therapy. The study is well designed and appropriately powered.

Reviewer: 2
Reviewer Name Hugo Partsch
Institution and Country Emeritus Professor of Dermatology
Medical University of Vienna
Austria
Please state any competing interests or state 'None declared': None declared

point 3 and 12:
initial therapy of DVT should be standardized among the centres

This is an excellent study concept which will provide important information about the value of individually tailored compression therapy after DVT to prevent PTS.

1. My main point of concern relates to the 6 weeks long inclusion period after the acute stage of DVT in which either no compression, compression by bandages or by stockings may be applied. These open treatment options for such a long time period may influence the outcome considerably. The initial management of DVT plays a deciding role for the inflammatory process involving the vein walls and the progression /regression of the clot, both of which are the basis for the development of PTS. In

order to avoid such confounding variables the study should start as early as possible after the acute event. The details of the conservative management of acute DVT including the strategy of anticoagulation, compression and mobilization needs to be standardized. A uniform protocol for the management of DVT among the centers is highly recommended.

Response:
We agree it is important that a uniform protocol for the management of DVT exists in all participating centers. This was not clearly described in the manuscript. In all participating centres there is a uniform protocol for all patients with a DVT, this was agreed upon for all patients (those eventually participating to the study and those who will or cannot participate).
In the initial acute phase after DVT, the leg is either bandaged (short stretch to compression 30-40 mmHg), or a bandage stocking (Struva 35®) is prescribed, or no compression is applied. In every hospital, one of these three (previously agreed upon) forms of therapy is applied in all patients in the acute phase.
When the acute oedema has been resorbed, usually within 2-6 weeks, a custom fitted elastic compression stocking (Mediven 550, 30-40 mmHg) is applied in all patients. Compression therapy with the elastic compression stocking is immediately started following the initial compression therapy, so there is no period without compression in between. The centers that do not apply initial bandaging start elastic compression stockings as soon as the edema is resorbed.
In summary, there is a uniform protocol for the management of DVT in all participating centres. Only the type of initial compression therapy in the acute phase is different per centre, this will give us the opportunity to assess the influence of compression in the acute phase on the development of PTS.
We changed this in the text, to clarify this.

[Changed in the text, page 6, lines 42-58, page 7 lines 2-7: There is a prespecified protocol for the management of DVT in all participating centres.
In the initial acute phase after DVT, until the acute oedema has disappeared, one of three strategies will be applied. The leg is either bandaged with short stretch bandages to a compression of 30-40 mmHg, worn day and night and redressed twice per week; or a bandage stocking with 35mmHg compression is prescribed (Mediven Struva 35 ®, Medi, Breda, the Netherlands), worn day and night; or no initial compression therapy is applied, according to the prespecified strategy of the participating center. After the initial phase, a custom fitted, flat knitted, knee length graduated elastic compression stocking class III (ankle pressure 40 mmHg) is prescribed for all patients. The same brand and type (Mediven 550) of compression stocking is prescribed to all patients in all participating centres. Compression therapy with the elastic compression stocking is started immediately after the initial phase, so there is no period without compression in between, with exception of the patients who do not receive compression in the initial phase.]

2. Assessments at any time point, including the first visit, should include the CEAP classification, at least concentrating on clinical signs (C). Both, Villalta scale and CEAP are non-specific for PTS and the assessment of changes should also include the initial stage at entry.

Response:
As the SSC recommended the use of the Villalta scale for defining the presence and severity of PTS, we choose to include the Villalta scale for the assessment of PTS during follow-up, and not the CEAP classification. (Kahn et al. Journal of Thrombosis and Haemostasis 2009; 7:879-883)
To keep the administrative burden for the participating physicians as low as possible we did not include both the Villalta scale and the CEAP classification.
We choose not to include assessment of the leg, with either the Villalta scale or the CEAP classification, at the first visit. The first visit takes place within 6 weeks after diagnosis and the acute signs of the DVT can be inappropriately attributed to PTS at that time. (Kahn et al. Journal of

Thrombosis and Haemostasis 2009; 7:879-883)

3. Outcomes: change of CEAP should be added as a secondary outcome (occurrence of skin changes!) and should also be checked at each follow up.
4. Additional objective parameters would be helpful. It would be easy to measure the circumference of both legs at predefined points in order to characterize leg swelling.
5. VAS or modified Lowenberg test to quantify pain should be considered.

Response:
Thank you for these valuable suggestions. We agree with you that collection of data on the CEAP score, leg circumference, VAS or modified Lowenberg, could improve the study.
However, in order for this study to succeed, the cooperation of all individual physicians to participate and keep participating is of great importance. Therefore, we tried to keep the administrative burden for the physicians as low as possible. Thus, inclusion of the CEAP classification, leg circumference, VAS or modified Lowenberg as an outcome or additional objective parameter was not feasible.

6. Basic Duplex data, at least followed every 12 months, would increase the scientific image of the study. It may be assumed that patients with initial reflux will have a higher risk of developing pathological Villata values in the following years, even when no clinical signs like varicose veins are present initially.

Response:
We choose not to measure reflux in this study. In the management study preceding this study no association between deep reflux and PTS was found. (Ten Cate-Hoek et al. Journal of Vascular Surgery 2010; 52:132-138) Therefore a standard duplex examination was not included in the study protocol.

7. Since the compliance of wearing the stockings is a major issue a diary given to the patients could be considered.

Response:
We agree that compliance of wearing stockings is a major problem. Compliance will be monitored by compliance questions (“do you wear the stocking?”, “how often do you wear the stocking?”, “if so: why do you not wear the stocking?”) in each questionnaire (5 questionnaires during 2 years) and by three random phone calls during follow-up, to check compliance and to address reasons for noncompliance. (see page 9, lines 7-26) A diary to be kept by the patient is a compliance enhancing intervention in itself, and could therefore bias the results of this pragmatic trial.

8. Some professional instruction for the patients how to apply and handle the stockings would improve compliance.

Response:
The stocking manufacturers that also fit the stocking provide instructions on how to apply and handle the stockings. Home care will be arranged in case a patient is not able to personally apply the stocking.

9. Stocking length and time of renewal need to be defined.

Response:
Stocking length is defined in the manuscript.(page 6, line 29) We agree that time of renewal should also be defined. Patients receive two new stockings every year. We added this in the text.

[Changed in the text, page 6, lines 54-58, page 7, lines 3-7: After the initial phase, a custom fitted, flat knitted, knee length graduated elastic compression stocking class III (ankle pressure 40 mmHg) is prescribed for all patients. The same brand (Mediven) and type of compression stocking is prescribed to all patients in all participating centres. Compression therapy with the elastic compression stocking is started immediately after the initial phase, so there is no period without compression in between, with exception of the patients who do not receive compression in the initial phase. Patients receive two new stockings every year.]

10. Since the dosage of compression is an essential part of therapy it would be advisable to measure the stocking -pressure at predefined points at least in a subgroup of patients (after application of a new stocking and before this is replaced by a new one).

Response:
The same brand and type of compression stocking is prescribed to all patients in all participating centres. We assume pressure properties of stockings of identical brand and type to be comparable, and therefore as well as for the sake of keeping the conduct of the study as simple as possible, did not include measurement of stocking pressure.

[Changed in the text, page 6, line 56-58: The same brand and type (Mediven 550) of compression stocking is prescribed to all patients in all participating centres.]

11. Since different brands of compression stockings have different elastic properties which may influence the outcome in addition to the resting pressure alone, it would be advisable that all centers use the same product.

See our response to comment 10.

12. Contraindication: intermittent claudication is a rather vague point, especially in DVT-patients who may have walking problems due to their underlying disease. Should be replaced by measurement of ABPI, e.g. excluding patients with an ABPI< 0.8.

Response:
We decided against formal diagnosis of intermittent claudication for this pragmatic trial. We exclude patients based on clinical signs and symptoms of arterial ischemia only; we do not measure ABPI and therefore have not stated the measurement of ABPI as exclusion criterion. In contrast to patients with primary venous insufficiency, patients with acute DVT usually do not have a history of walking problems due to venous disease. Furthermore, we exclude patients with pre-existing oedema for which elastic compression therapy was installed preceding the acute DVT, and in addition we also exclude patients that already have skin changes due to long-time existing increased venous pressure.

13. The three scenarios described do not take into account that there might be also a worsening after initial improvement, in accordance with the concept of a “latency period”. Would such a case stay untreated up to two years?

Response:
After the initial acute phase an elastic compression stocking is prescribed to all patients.
Patients randomized to the control group (standard duration of 2 years ECS therapy) wear the stocking for a duration of 2 years.
Patients randomized to the intervention group (individually tailored duration of ECS therapy) wear the stocking for a minimum duration of 6 months. After the first 6 months (dis)continuation of wearing the

stocking is decided based upon the Villalta scores at three and six months.
If a patient develops complaints after discontinuation of the stocking, a predefined protocol is followed. When a recurrent DVT is improbable or excluded, the patient is advised to wear the stocking for a period of a week. When the complaints do not improve after a week, the patient is advised to resume wearing the stocking.

[Deleted: Once stopped, ECS treatment will not be reinstated.]

[Changed in the text, page 8, lines 21-23: When a patient develops symptoms and signs of PTS after discontinuation of ECS therapy, a predefined protocol is followed. If necessary, ECS treatment will be reinstated.]

Reviewer: 3
Reviewer Name Susan Kahn
Institution and Country McGill University, Montreal, Canada
Please state any competing interests or state 'None declared': None declared

This manuscript describes a clinical trial protocol of the IDEAL study, an RCT of individualized duration elastic compression therapy vs. long term duration elastic compression stockings (ECS) therapy for prevention of post-thrombotic syndrome. The role of ECS in both PTS prevention and treatment is as yet unclear, particularly in light of a recently published multicentre placebo-controlled RCT suggesting that ECS are not of benefit to prevent PTS, hence this is a clinically relevant study.

Critique/suggestions:

1. Title: change 'against' to 'versus'

Response:
Thank you for the suggestion. We have used the word "against "solely for the sake of the acronym.

Abstract:
2. Last line of Methods and analysis: change 'after' 24 months to 'at' 24 months.

Response:
As requested we changed 'after' to 'at'.

[Changed in the text, page 2, lines 37-39: The primary outcome is the proportion of patients with PTS at 24 months.]

3. Under Ethics and dissemination: unclear what "broad application" means- clarify.

Response:
It is meant to say that the widespread standard application of elastic compression stockings in all patients after DVT is questioned. We changed "broad" into "standard" to make this sentence more clear.

[Changed in the text, page 2, line 44: Based on current knowledge the standard application of ECS therapy is questioned.]

4. It is unusual to have a subheading "Ethics and dissemination" in a manuscript abstract. Could change to Clinical relevance

Response:
BMJ open obliges protocol papers to include the subheading “Ethics and dissemination” in the abstract.

Manuscript:
5. Background: I found the background section to be disorganized and the argument building up to the need for the IDEAL Trial was not as clear as it could be. What is the overall specific aim of the IDEAL trial? What are the primary and secondary objectives, and why?

Response:
Thank you for the critical reading of the manuscript. We have tried to (re)organize the text and put more emphasis on the specific aim of the trial as well as on the objectives.

6. Give number of patients studied in “our management study” (p3 line 47). What were the limitations of the management study such that a multicentre trial was needed?

Response:
Thank you for this suggestion.
The management study had a population of 125 patients. It was not a randomized trial, but a prospective management cohort study. The study had an open character and therefore prone to bias. A randomized controlled trial with an adequate sample size was needed to confirm the safety and effectiveness of individually tailored ECS therapy.

[Changed in the text, page 3, lines 23-38: We have previously assessed the safety of shortened duration of ECS therapy based on individual patient clinical scores in a management study of 125 patients, and we have shown that tailoring the duration of ECS therapy based on the signs and symptoms of the individual patient after an initial treatment period of 6 months, is a safe strategy to prevent PTS. We found that 50% of our patients did not need ECS therapy for as long as 2 years, while the overall incidence of PTS was 21.1% (95% CI 13.5- 28.7).[9] This incidence is comparable to published incidences after 24 months ECS therapy.[7 8] While this was a prospective management cohort study with an open character and therefore prone to bias, the results of this study need to be confirmed by an adequately powered randomized controlled trial.]

7. What type of currency is being described on p 4 line 8 and 9 (ie dollars? Euros?)

Response:
The currency described is Euros.

[Added, page 5 lines 20-22: Total annual costs of ECS therapy roughly amounts to 2.5 million euro for stockings (25.000 patients*100 euro) and 21 million euro for home care (7.5%*25.000 patients*500 visits*20 euro).]

8. Unclear if p4 lines 25-30 refer to the IDEAL trial (re: we will perform…).

Response:
We will perform refers to the IDEAL DVT study. We changed the text to make this more clear.

[Changed in text, page 4, lines 47-57, page 5, lines 3-7: The IDEAL DVT study aims to address these topics. In addition quality of life, patient preference towards ECS therapy, compliance to therapy, as well as cost-effectiveness of ECS therapy will be assessed.

The primary outcome of the IDEAL DVT study will be PTS at 24 months after the event. The secondary outcomes will be: 1. Health Related Quality Of Life, measured by questionnaires (SF-36[13], EuroQOL-5D[14], Dutch translated Veines-Qol[15], 2. Costs[16], 3. Recurrent thrombosis, according to criteria as published[17] and assessed by objective tests, 4. VTE related death during follow-up, assessed by an independent and blinded adjudication committee, 5. Patient preferences, assessed with a Discrete Choice Experiment (DCE)[18].]

9. Avoid use of “broad” application- this is not correct English.

Response:
Thank you for this suggestion, we changed this in the text.

[Changed, page 4, lines 40-42: Based on current knowledge it is therefore understood that the standard application of ECS therapy is questioned.]

[Changed in the text, page 12, line 16: Based on current knowledge the standard application of ECS therapy after DVT is questioned.]

10. Methods/design: Change “fair” to balanced. (p4 line 54).

Response:
Thank you for this suggestion, we changed this in the text.

[Changed in text, page 5, lines 34-36: Randomization will guarantee a balanced distribution of patients within each patient group.]

11. It is not well explained why you are stratifying for age sex and BMI. Also, BMI is a continuous variable- thus, how do you stratify for BMI? Are you using BMI ‘bands’? If yes, bands of what width?

Response:
We stratify for age, sex, and BMI because these have all been described as risk factors for developing PTS. (Ageno et al. Thomb Haemost. 2003 89:305-309, Kahn et al. Journal of Thrombosis and Haemostasis. 2005 3:718-723, Schulman et al. Journal of Thrombosis and Haemostasis. 2006 4:734-742, Tick et al. Journal of Thrombosis and Haemostasis. 2008 6:2075-2081) Therefore we want age, sex and BMI to be equally distributed over the two treatment groups.
BMI is stratified as BMI <26 kg/m2 or BMI ≥26 kg/m2. We clarified this in the text.

[Changed in text, page 7, lines 19-25: A web-based randomisation program (TENALEA (Trans European Network for Clinical Trials Services)) is used that executes blocked randomisation with stratification on centre-level and on possible confounding patient characteristics such as age, sex, and Body Mass Index (<26 kg/m2 - ≥26 kg/m2).]

12. P5 line 4: It is stated that the primary outcome is PTS at 24 months after DVT, but from the analysis it appears to be PTS within 24 months of DVT – clarify

Response:
The primary outcome is the proportion of patients with PTS at the end of follow-up, 24 months after DVT. We do assess the difference in percentage of PTS between the individually tailored group and the standard treatment group. We however analyse the cumulative probability of PTS and therefore one could strictly speaking better use the wording “within 24 months”. If a patient is diagnosed with PTS, either at 6 months after DVT or at 12 months after DVT, he or she will still have PTS at 24 months, as PTS is a chronic condition.

13. P5 line 26: are patients being included within 6 weeks after DVT? A critique of some previous ECS trials is that the ECS were not applied quickly enough- 6 weeks seems like a long time-justify. In fact, need to make it more clear throughout paper what is the timepoint of inclusion/randomization- at DVT diagnosis? After 6 months of use of ECS?

Response:
In all participating centres there is a prespecified protocol to treat patients with a DVT.
In the initial acute phase after DVT, the leg is either bandaged, or a bandage stocking is prescribed, or no compression is applied. In every hospital, one of these three forms of therapy is applied in all patients in the acute phase.
When the acute oedema has been resorbed, usually within 2-6 weeks, a custom fitted elastic compression stocking is fitted in all patients. After the compression therapy in the acute phase, compression therapy with the elastic compression stocking is immediately started, so there is no period without compression in between.

Inclusion takes place at the first visit to the outpatient clinic, usually within 2 weeks but no later than 6 weeks after DVT diagnosis. Subsequently, within 1-3 days after inclusion, randomization takes place in the coordinating centre. We changed the text to make this more clear.

[Changed in text, page 6, lines 5-10: Consecutive, consenting adults with an acute objectively documented proximal DVT of the leg, adequately treated with anticoagulant treatment and initial compression therapy according to a prespecified protocol are included in the study. Patients are included and randomized in to the IDEAL DVT study within 2-6 weeks after DVT.]

[Changed in the text, page 6, lines 42-58, page 7 lines 3-7: There is a prespecified protocol for the management of DVT in all participating centres.
In the initial acute phase after DVT, until the acute oedema has disappeared, one of three strategies will be applied. The leg is either bandaged with short stretch bandages to a compression of 30-40 mmHg, worn day and night and redressed twice per week; or a bandage stocking with 35mmHg compression is prescribed (Mediven Struva 35 ®, Medi, Breda, the Netherlands), worn day and night; or no initial compression therapy is applied, according to the prespecified strategy of the participating center. After the initial phase, a custom fitted, flat knitted, knee length graduated elastic compression stocking class III (ankle pressure 40 mmHg) is prescribed for all patients. The same brand and type (Mediven 550) of compression stocking is prescribed to all patients in all participating centres. Compression therapy with the elastic compression stocking is started immediately after the initial phase, so there is no period without compression in between, with exception of the patients who do not receive compression in the initial phase.]

14. P6 line 26: If you exclude patients who develop recurrent DVT within 6 months follow-up, this is post randomization exclusion and contravenes the ITT analysis principle- need to justify.

Response:
Patients that develop a recurrent ipsilateral DVT within 6 month follow-up are excluded, because it is not justified to advise these patients to take off their stocking after 6 months.
You are right that excluding patients from the analysis after randomization contravenes the ITT analysis principle. However, we do not expect that this will influence our results, as treatment in the two groups only begins to differ after 6 months. During the first 6 months all patients will wear the elastic compression stocking.

15. Why do you exclude patients with pre-existing CVI- these may be patients most likely to benefit from stockings. I suggest for the readers' sake that you provide a brief rationale for all the exclusion

criteria.

Response:
Patients with pre-existing CVI have an increased risk of developing PTS. (Tick et al. Journal of Thrombosis and Haemostasis. 2008; 6:2075-2081, Ten Cate-Hoek et al. Journal of Vascular Surgery. 2010; 52:132-138) In addition, a lot of these patients already wear elastic compression stockings, before developing a DVT. It would not be wise to discontinue stocking therapy in these patients, and most of the patients who already chronically wear stockings are not willing to discontinue stocking therapy.
Furthermore, patients with pre-existing CVI will already score high on the subjective symptoms and objective signs of the Villalta scale, even before having had a DVT. Because PTS and CVI are closely related, it is difficult to differentiate CVI from PTS, with the risk of misclassification.
Therefore we decided not to include these patients.

We added a brief rationale for all exclusion criteria. Thank you for this suggestion to improve the manuscript.

[Changed in the text, page 6, lines 12-38:
Exclusion criteria are:
• Previous DVT in the affected leg. Patients with a previous ipsilateral DVT might already have developed PTS after the first DVT.
• Recurrent DVT in the 6 months following inclusion, as it cannot be justified to advise these patients to discontinue ECS therapy 6 months after DVT.
• Pre-existent venous insufficiency (skin signs C3-C6 on CEAP score or requiring ECS therapy). Pre-existent venous insufficiency increases the risk of developing PTS and the majority of patients with venous insufficiency already chronically wear elastic compression stockings. In addition venous insufficiency is closely related to PTS and is therefore difficult to differentiate from PTS.
• Contraindication for ECS therapy such as intermittent claudication or clinical signs of leg ischemia or asymptomatic arterial insufficiency (a pulse deficit or bruit at sites of narrowing at physical examination).,
• Active thrombolysis, as thrombolysis reduces the risk of PTS.
• Limited life expectancy (< 6 months), as the follow-up period is 2 years.]

16. Page 6 line 14: Is it considered ethically acceptable for the coordinating centre in Maastricht to contact patients directly to inform them of their allocation group? Do patients provide consent for this, specifically? In North America it would not be allowed for someone outside the patient's treating centre to be given patient identifying information and to directly contact the patient.

Response:
In the Netherlands it is allowed for the coordinating centre to contact the patients directly, when the patients have given informed consent to participate in the study (informed consent is provided in their treating centre). This is part of the consent they give for participating in the study.

17. P6 line 51: "Once stopped, ECS will not be reinstated"-what if a patient develops symptoms of PTS? How can one justify not reinstating ECS to control symptoms if PTS develops?

Response:
After the initial acute phase an elastic compression stocking is prescribed to all patients.
Patients randomized to the control group (standard duration of 2 years ECS therapy) wear the stocking for a duration of 2 years.
Patients randomized to the intervention group (individually tailored duration of ECS therapy) wear the

stocking for a minimum duration of 6 months. After the first 6 months (dis)continuation of wearing the stocking is decided based upon the Villalta scores at three and six months.
If a patient develops complaints after discontinuation of the stocking, a predefined protocol is followed. When a recurrent DVT is improbable or excluded, the patient is advised to wear the stocking for a period of a week. When the complaints do not improve after a week, the patient is advised to resume wearing the stocking.

[Deleted: Once stopped, ECS treatment will not be reinstated.]

[Changed in the text, page 8, lines 21-23: When a patient develops symptoms and signs of PTS after discontinuation of ECS therapy, a predefined protocol is followed. If necessary, ECS treatment will be reinstated.]

18. P. 7 line 41. What is the hypothesis concerning the patient preferences DCE substudy? How many patients will receive the DCE questionnaire, and how will data be analysed/interpreted. If the trial's main result shows lack of non-inferiority of individually tailored ECS but patients prefer not to wear ECS based on DCE substudy, how will the overall results be interpreted? Suggest providing more details on the rationale for and interpretation of this interesting substudy.

Response:
The hypothesis of the DCE is that patients make trade-offs based on the characteristics of ECS therapy when deciding to wear or not to wear the elastic compression stocking.
Conducting a DCE will hopefully give us insight in these trade-offs, of which duration of ECS therapy is one. The results of the DCE sub study do not influence the main results of the study, but merely inform on the patient's motivations for compliance or non-compliance. The results of the DCE study could be helpful in future practice to help anticipate on these trade-offs and specifically inform or educate patients on subjects that matter to them most.
300 patients will receive the DCE questionnaire.
The data will be analysed using Nlogit econometric software.
We added some more details on the rationale and interpretation of the DCE.

[Changed/Added, page 10, lines 34-44: ECS therapy has several disadvantages for the patients (stockings are uncomfortable, ugly, and difficult to put on and off), while duration and effectiveness are uncertain. A DCE will be conducted to assess the patient preferences regarding ECS therapy, providing insight in the trade-offs patients make between characteristics of the therapy when deciding to wear the stocking or not. Duration of ECS therapy is one of the characteristics. Data will be analysed using multinomial logit models and mixed logit models.(Nlogit, Econometric Software)]

19. P8 line 7: Crossover sentence is unclear- in what situations might crossover occur? If patients whose ECS were discontinued early (in experimental arm) later develop symptomatic PTS, wouldn't there be an obligation to instate ECS for symptom control? Will such "off label" ECS use be systematically tracked and reported?

Response:
Crossover can occur in three situations:
- Patients randomized to the control group (standard duration of 2 years elastic compression stockings) do not wear the stocking.
- Patients randomized to the intervention group (individually tailored duration of ECS therapy) who have to continue wearing the stocking (based on their Villalta score), do not wear the stocking.
- Patients randomized to the intervention group (individually tailored duration of ECS therapy) who are instructed to discontinue wearing the stocking, do acutually wear the stocking.
The compliance checks of the study will also give insight in crossover and reasons for crossover.

Compliance will be monitored by compliance questions (“do you wear the stocking?”, “how often do you wear the stocking?”, “if so: why do you not wear the stocking?”) in each questionnaire (5 questionnaires during 2 years) and by three random phone calls during follow-up, to check compliance and to address reasons for noncompliance.
As described in the answer to question 17, in case symptoms and signs of PTS after discontinuation of ECS therapy, ECS therapy will be reinstated. The latter case will not be considered noncompliance.

20. What is the hypothesis with regard to the cost utility analysis?

Response:
The hypothesis of the cost utility analysis is that individually tailored duration of ECS therapy will be cost-effective compared to standard duration of 2 years elastic compression stocking therapy. More specifically, we expect individually tailored ECS therapy to be cheaper with an acceptable small or no loss of quality adjusted life years.
Since duration of ECS therapy is expected to be reduced in a proportion of the patients in the individually tailored duration ECS therapy group, costs will be saved (costs of stockings and costs of home care for application of stockings).

21. Sample size calculation- it is unclear if the 7.5% difference represents the upper bound of the confidence interval of difference in rates of PTS between groups, or rather the point estimate. If the latter, what is the upper bound of the CI? Unclear what is meant by “this proportion of loss in efficacy is customarily accepted….”-clarify and provide a reference.

Response:
The non-inferiority margin of 7,5% is the maximum accepted difference in effectiveness between the standard treatment (2 years elastic compression stocking therapy) and the new treatment (individually tailored duration of elastic compression stocking therapy), to be able to conclude that the new treatment is non-inferior to the standard treatment. This 7,5% represents the upper bound of the confidence interval of difference in rates of PTS between the two groups. As pointed out in the guideline by the International Conference on Harmonization (ICH), the determination of noninferiority margins should be based on both statistical reasoning and clinical judgment (e.g.safety,cost/benefit analysis). There are no formal referenced detailed criteria (gold standard) for determination of non-inferiority margins in trials for various categories of medications or treatments and therefore we cannot provide these references. The sentence “the proportion of loss in efficacy is customarily accepted” refers to current literature in which examples of retained treatment effects between 50%-80% are described as acceptable for the choice of delta. (H.R. Büller et al. The New England Journal of Medicine. 2013;369:1406-1415, sample size based on retention of treatment effect of at least 70%; S. Schulman The New England Journal of Medicine. 2013;368:709-718, sample size based on retention of 70% of the treatment effect)

22. A 2% rate of loss to follow in a trial of 2 years duration seems overly optimistic, especially as patients with cancer are not explicitly excluded from participating. Can the authors provide justification based on previous similar trials (with supporting references)?

Response:
With loss to follow up we indicate patients that are not participating in the study anymore and are not traceable. Patients who die during follow-up are therefore strictly speaking not lost to follow-up. To minimize the (expected) loss due to mortality patients with cancer although not excluded as a group, are excluded on an individual basis if they have a life expectancy of <6 months .
In the studies of Prandoni (Prandoni et al. Annals of Internal medicine 2004) and Brandjes (Brandjes et al. Lancet 1997) on ECS therapy the percentage of loss-to-follow-up was 1,1% and 3,1% respectively. The 2% loss-to-follow-up is nicely in between these figures.

23. If 2 consecutive + Villalta scores are required to diagnosis PTS, in the time to event analysis, which timepoint will be attributed as the timepoint of PTS development- the first, or the second? This should be stated.

Response:
A patient is diagnosed with PTS if he or she has two Villalta scores of ≥5 on two consecutive visits that were at least three months apart. Hence, the diagnosis can only be made after the second Villalta score of ≥5. Therefore, the second time point will be attributed as the time point of PTS development. We added this in the method section.

[Changed in text, page 9, lines 35-37: The time point of the second Villalta score of ≥5 will be considered the time point of PTS diagnosis.]

24. The analysis section requires more details- how will the QOL and DCE data be analysed?

Response:
We agree with you that this section requires some more details, and we added some more details on the analyses of the QOL and DCE data.

[Added, page 10, lines 27-32: Incremental cost-utility ratios will be calculated, and non-parametric bootstrap analyses will be used to quantify the uncertainty surrounding the cost-utility ratio of the trial-based analysis. Sensitivity analyses and subgroup analyses will be performed, to assess the impact of variation in parameters and heterogeneity of the patient population.]

[Added, page 10, lines 42-44: Data will be analysed using multinomial logit models and mixed logit models.(Nlogit, Econometric Software)]

25. The ANOVA sentence is quite vague.

Response:
It is meant that we will compare several outcome measures (individual Villalta scores, quality of life etc.) at the different time points of follow-up.
We changed the text to make this more clear.

[Changed in text, page 11, lines 32-36: ANOVA will be applied to assess changes over time, by comparing different outcome measures at the different time points of follow-up.]

26. Why adjust for age and sex (both are stratification variables) but not BMI (also a stratification variable). Will you adjust for centre-this is also a stratification variable, as per Methods.

Response:
A cox regression model is used to predict the probability of the event of interest at a given time t for given values of the predictor variables. We agree with you that, since BMI is also a stratification variable, we should include this as a predictor variable. We will not adjust but stratify for centre, to avoid excessive dummy variables.
We changed this in the text of the article.

[Changed in text, page 11, lines 40-42: Hazard ratio's will be stratified for centre and adjusted for age, sex, BMI, clinical presentation of DVT, and extent of the index deep vein thrombosis.]

27. How will the results be interpreted? If there are no differences between groups in the 2-year

cumulative incidence of PTS, how will you be able to determine that this is because individually tailored ECS are as effective (ie non-inferior) to 2 years of ECS- it could also be interpreted that ECS, whether individually tailored or worn for 2 years, equally do not influence the risk of PTS- ie no effect of either intervention. As all patients receive ECS (for varying durations), if individually tailored ECS are as effective (ie non-inferior) to 2 years of ECS, couldn't the explanation be that ECS palliated symptoms of PTS in patients who were destined to develop PTS, and were not needed in patients who didn't develop PTS? That is, how will you distinguish whether ECS prevented PTS versus palliated symptoms of existing PTS, in those patients who developed PTS?

Response:
We aim to assess the non-inferiority of individually tailored ECS therapy versus standard 2 years ECS therapy. If the PTS incidence is not different between the two groups or the difference does not exceed the non-inferiority margin, we can conclude that individually tailored ECS therapy is as good as 2 years ECS therapy.
This is no placebo controlled trial, so we cannot exclude a placebo effect. One can indeed argue that the found effect of both treatment groups can be attributed to a placebo effect, or a palliation in those patients destined to develop PTS while the stocking did not have an effect in the patients who did not develop PTS.
As described in the background of the manuscript, so far three randomized trials have been performed on this subject, of which two show a clear effect of ECS therapy in the prevention of PTS (Brandjes et al. The Lancet 1997 349:759-762, Prandoni et al. Annals of Internal Medicine 2004; 141:249-256), while one does not show superiority of active ECS compared over placebo ECS (Kahn et al. Lancet 2013; 383:880-888). We will interpret the results generated by this study within the spectrum of the body of evidence present so far.

28. Ethical considerations: please indicate if the participating centres ethics committees (both in Italy and the Netherlands) approved the study, not just the coordinating centre's ethic committee.

Response:
In the Netherlands the ethics committee of the coordinating centre provides overall ethical approval of the study protocol. The participating centres gained approval of their ethical boards for the local feasibility of the study in the hospital. In Italy the protocol was approved by the Ethical Board of the University Hospitals of Padua and Treviso.We added this in the text as suggested.

[Changed in text, page 12, lines 6-10: The medical ethical committees of all participating hospitals in the Netherlands and Italy approved this study.]

29. The SOX Trial is criticized for imperfect compliance- it would be more balanced to add that a per protocol analysis of frequent ECS users was consistent with the main analysis in showing no effect of ECS.

Response:
We have put our criticism in perspective by adding the statement about the per protocol analysis, as suggested.

[Changed in text, page 4, lines 29-38: The compliance to ECS therapy, a major determinant of effectiveness, was 55.6% after 24 months. This was less in comparison to the previous trials by Brandjes and Prandoni, where compliance was up to 90%. Although a per protocol analysis of the patients reporting regular stocking use yielded the same outcome, this sub analysis may not be adequately powered to dismiss lack of compliance as an important determinant of non-effectiveness.]

30. Last sentence: when is the study expected to complete recruitment, and thus when are results expected? This information would be helpful to the reader.

Response:
Thank you for this suggestion, we added this in the text of the manuscript.

[Changed in text, page 12, lines 34-36: The IDEAL DVT study started including patients March 2011 and is currently on-going. Recruitment is expected to be terminated within 1 year. As the follow-up is 2 years, the results are expected within 3 years.]

VERSION 2 – REVIEW

REVIEWER	Hugo Partsch, M.D. Emeritus Professor Medical University of Vienna, Austria
REVIEW RETURNED	14-Jun-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	Susan Kahn McGill University, Canada
REVIEW RETURNED	24-May-2014

GENERAL COMMENTS	The paper is considerably improved and I have no further comments.

VERSION 2 – AUTHOR RESPONSE

We again thank the reviewers for their careful reading of the manuscript and their highly insightful suggestions, which enabled us to improve the manuscript.