Amsterdam UMC
University Medical Centers

Statistical analysis plan for the Dutch Injection versus Surgery TRIal in Carpal Tunnel Syndrome Patients (DISTRICTS)

NB: For this statistical analysis plan (SAP) the following template was used: Clinical Research Unit Version 1.1, 10-JUL-2019.

Section 1a. Title.

What is the title of the statistical analysis plan?

Statistical analysis plan for the Dutch Injection versus Surgery TRIal in Carpal Tunnel Syndrome patients (DISTRICTS): a multicenter open-label randomized controlled trial comparing two treatment strategies.

Section 1b. Names and Signatures.

What are the names, affiliations and roles of contributors to this statistical analysis plan?

Role of contributor	Name and full affiliation	Signature	Date of signature
Principal investigators	Dr. C. Verhamme	C Verhamme	17-JUL-2023
	Prof. dr. R.M.A. de Bie		17-JUL-2023
Researcher(s) who will perform the statistical analysis	Drs. W.A.C. Palmbergen		20-07-2023
	Dr. A.M. Heeren		17-Jul-2023
Senior statistician consulted	Dr. J.A. Bogaards	JaB	17-JUL-2013
Contributors to statistical analysis plan	Dr. C.A.J.M. de Borgie		18-Jul-2023

Section 1c. Revision history of the statistical analysis plan.

What versions of the statistical analysis plan have been approved and filed and what was the reason for producing each version?

Not applicable.

Updated statistical analysis plan version	Protocol version	Section number(s) changed	Description of and reason for changes	Date of approval

Section 1d. Administrative Information.

1.1. What is the trial registration number?

This study is registered in the primary clinical trial registry recognized by WHO and ICMJE under reference ISRCTN13164336.

1.2. What is the planned period of observation?

The date of the inclusion of the first patient was 07-NOV-2017. The completion of follow-up for the last patient is 07-JUN-2023.

1.3. What is the date and version number of the current statistical analysis plan?

This is the first version of the Statistical Analysis Plan (SAP) for the DISTRICTS study.

1.4. What is the date, version number and reference number of the protocol used when writing this statistical analysis plan?

This SAP is based on the protocol with reference number NL61506.018.17 version 5.0 dated 29-JAN-2018.

Section 2. Introduction.

2.1. What is the background and rationale for the study?

Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy. The optimal treatment strategy is still unknown. This results in considerable practice variation in the treatment of CTS.
For further details on the background and rationale of this study please see the study protocol.

2.2. What are the objectives of the study?

The objective of the DISTRICTS study is to compare the clinical effectiveness and cost-effectiveness of a treatment strategy for CTS starting with surgery compared with a treatment strategy starting with a corticosteroid injection.

Primary objective:
The primary objective is to assess if the treatment strategy for CTS starting with surgery results in a higher proportion of participants recovered after 18 months follow-up since randomization when compared to the treatment strategy starting with a corticosteroid injection.

Secondary objectives:
To compare the treatment strategy for CTS starting with surgery with the treatment strategy starting with a corticosteroid injection regarding:

A. time to recovery during 18 months follow-up;
B. proportion of participants recovered at different time points during 18 months follow-up;
C. symptom severity at different time points during 18 months follow-up;
D. upper limb functioning after 18 months follow-up;
E. scar or palm pain at different time points during 18 months follow-up;
F. participant's global perception of recovery after 18 months follow-up;
G. participant's satisfaction after 18 months follow-up;
H. health-related quality of life after 18 months follow-up;
I. number of additional treatments during 18 months follow-up;
J. number of adverse events during 18 months follow-up;
K. the cost-effectiveness and cost-utility from a societal perspective after 18 months follow-up (the economic evaluation is elaborated in a health economic analysis plan (HEAP)).

Section 3. Study Methods.

For consistency, the following sections are written in the past sense, also regarding matters in the (near) future.

3.1. What is the study design?

The DISTRICTS study was an investigator-initiated, multi-center, open-label randomized controlled trial comparing two treatment strategies for CTS. The study had two arms; a treatment strategy starting with surgery (surgery group) and a treatment strategy starting with a corticosteroid injection (injection group). If needed, these treatments could be followed by any additional treatments within the 18 months follow-up. For further details please see Page 15 of the study protocol (version 5.0).

3.2. Will randomization be performed in this study?

In this study, 941 patients were randomized by local clinicians using a centralized web-based application (ALEA Clinical software, FormsVision B.V., The Netherlands) in a 1:1 ratio and stratified by type of CTS symptoms (unilateral or bilateral), secondary CTS due to a known underlying cause (yes or no), and a history of previous ipsilateral CTS injections more than one year ago (yes or no), using variable permuted blocks with block sizes of two, four, six, and eight. Randomization was not stratified by center.

This was an open label study.

3.3. How was the sample size calculated?

No reliable data were available regarding recovery in case of strategies that included different treatments. Therefore, we conservatively estimated that after 18 months 70% of patients in the surgery group and 60% of patients in the injection group would be recovered.[1,2] A difference in recovery after 18 months of 10% was considered a minimal clinically important difference. A Fisher's exact test with a 0.05 two-sided significance level would have 80% power to detect the difference between a proportion of 0.70 (recovery in surgery group) and a proportion of 0.60 (recovery in injection group) when the sample size in each group is 376 (752 patients in total). Anticipating a 20% attrition rate, we aimed to include (376 / 0.80 =) 470 patients per treatment group; 940 patients in total. This sample size calculation was performed using nQuery Advisor (Statistical Solutions Ltd., United States of America).

References:
[1] Meys *et al.* Prognostic factors in carpal tunnel syndrome treated with a corticosteroid injection. Muscle Nerve 2011;44(5):763-8.
[2] Bland *et al.* Treatment of carpal tunnel syndrome. Muscle Nerve 2007;36(2):167-71.

3.4. What is the hypothesis testing framework for this study?

The DISTRICTS study used a superiority hypothesis testing framework for the primary outcome.

3.5. Will interim analyses be performed in this study?

No interim analyses were performed and there were no statistical or clinical guidelines for stopping the DISTRICTS study early.

3.6. When will the final statistical analysis of the study data be performed?

The statistical analysis of the primary outcome and reporting of all secondary outcomes were performed after completing the 18-month follow-up visit of the last included patient, and after data cleaning and database lock for these outcomes. The final patient was included in the study in November 2021. The follow-up was completed in June 2023. We expected that the final statistical analyses for these outcomes were completed before January 2024.

3.7. At which time points are the outcomes measured?

After inclusion and before randomization baseline characteristics were collected. The time points for outcome measurements were six weeks, and three, six, nine, 12, 15, and 18 months after randomization. For outcome measurements, paper or digital self-report questionnaires were used.

Paper questionnaires were sent one to two weeks before the upcoming follow-up time point. If the questionnaires were not returned within two weeks, a reminder and new questionnaires were sent. Digital questionnaires were sent automatically at the day of the follow-up time point. If the digital questionnaires were not completed within two weeks, a reminder was sent automatically by e-mail.

For both paper and digital questionnaires applied: if there was still no response one week after the reminder, the patient was contacted by telephone. Trained personnel contacted the patient and assessed the reason for not returning the questionnaires and asked if the patient would be willing to continue follow-up assessments, and if not, the patient was asked to complete the last follow-up questionnaires after 18 months follow-up only. If the patient agreed, the questionnaires were completed by telephone.

In case telephone contact could not be established questionnaires was sent at the next follow-up time point. A patient was considered a drop-out if a patient stopped participation due to withdrawal of consent, serious illness hindering participation and death; these reasons were registered separately (as also defined in 5.4).
Nota bene: If the patient did not fill in the date of the completion of the questionnaires, the date of receipt was registered.

Section 4. Statistical Principles.

4.1. Which level or levels of statistical significance will be used in the study?

The primary outcome was considered statistically significantly different between the surgery group and the injection group if the two-sided p-value was less than 0.05.

For the secondary outcomes, formal statistical tests were not performed to examine differences between the surgery group and the injection group. Differences between the treatment groups with regard to the secondary outcomes measured at single time points were summarized using appropriate parameters with their corresponding 95% confidence intervals (CIs). Differences between the surgery group and the injection group with respect to repeatedly measured outcomes were analyzed using a generalized linear mixed effect model with treatment group as a fixed-effect and an appropriate random effect structure.

4.2. Will the analysis adjust for multiplicity of statistical testing to ensure control of type I error rate?

Because there was only one primary outcome, measured at a single time point, the analysis did not adjust for multiplicity of statistical testing.

4.3. Which confidence intervals will be reported?

In all analyses, statistical uncertainty was expressed in two-sided 95% CIs of estimated parameters.

4.4. How is compliance defined and assessed?

Compliance was defined as the proportion of participants with informed consent that received the allocated initial treatment (*i.e.*, surgery or a corticosteroid injection) within six weeks after randomization.

4.5. How will compliance be presented?

Compliance was reported as the proportion of participants that received the allocated treatment per treatment group and the proportion of participants that received the allocated treatment within six weeks after randomization per treatment group.

4.6. What are defined as protocol deviations in this study?

Protocol deviations were defined as:

- deviations from the eligibility criteria;
- failure to administer the allocated initial treatment (*i.e.*, surgery or a corticosteroid injection) within six weeks after randomization.

4.7. How will protocol deviations be presented in the reporting of this study?

All protocol deviations were line-listed according to treatment group (*i.e.*, surgery group and injection group). In addition, the number and the proportion of participants in each treatment group with one or more protocol deviations were presented.

4.8. Which analysis populations will be defined?

The intention-to-treat (ITT) population included all randomized patients who gave informed consent, regardless of protocol deviations.

For the as treated analysis, patients were categorized according to the actual first treatment they received. The as treated population included all patients who met the following three criteria: provided informed consent, received surgery or a corticosteroid injection within six weeks after randomization, and provided the primary endpoint after 18 months follow-up. At each follow-up visit, patients filled in which hand had received the study treatment (*i.e.*, left or right) and responded to the questions for that hand. Recording the correct hand at 18 months was a prerequisite to consider the primary endpoint available.

Section 5. Study populations.

5.1. Which data were collected from participants, who were screened for eligibility for inclusion in the study, and how will these data be presented in study reports?

All recruiting hospitals were asked to record the following screening data: the number of CTS-patients screened, the number fulfilling the inclusion criteria, the number willing to participate, the number not willing to participate, and the reasons for declining participation. Eight recruiting hospitals collected the screening data. The other 25 hospitals were not able to record these screening data due to logistical complexity.

Reasons for no participation were categorized as follows:

1. did not want surgery or an injection,
2. did not want surgery,
3. did not want an injection,
4. no interest in trial participation, and
5. other (including second opinion/time to overthink participation) or unknown reasons.

These data were included in the Consolidated Standards of Reporting Trials (CONSORT) study flow diagram (See Appendix Figure 1).

5.2. What are the inclusion and exclusion criteria for the study?

The inclusion criteria were:

- age 18 years or older;
- clinically suspected CTS, which was confirmed by electrophysiological or sonographic testing;
- surgery and a corticosteroid injection were both considered by the neurologist as potential treatment options;
- the symptoms of CTS had to be present for at least six weeks;
- treatment intended to be given within six weeks following randomization;
- patients could participate with the most affected hand only in case both hands were eligible.

Exclusion criteria were:

- previous CTS surgery on the ipsilateral wrist;
- a corticosteroid injection for CTS in the ipsilateral wrist less than one year ago;
- previous participation in the DISTRICTS study;
- clinical or neurophysiological findings that suggested the symptoms were due to another diagnosis;
- not able to comprehend Dutch self-report questionnaires;
- pregnancy;
- follow-up not possible;
- legally incompetent adults;
- no informed consent.

Please see Chapter 4 on Pages 13-14 of the study protocol (version 5.0) for an overview of the inclusion and exclusion criteria of the DISTRICTS study.

5.3. Which information will be presented in the flow chart for this study?

The mock-up of the CONSORT flow diagram is presented in the Appendix (Figure 1) to this SAP.

5.4. What is the expected level of, timing of and reasons for withdrawal from the intervention and/or from follow-up and how will this be presented in the study reports?

When planning the study, we anticipated a 20% attrition rate.
We reported the number of unavailable measurements for each time point of each study arm (*i.e.*, surgery group and injection group).

Reasons for unavailable measurements:

- did not return questionnaires;
- lost to follow-up;
- withdrew consent;
- stopped participation due to serious illness; and
- deceased during follow-up.

A patient was considered lost to follow-up if there was no contact with the patient leading to an unavailable 18 months measurement beginning from the first unavailable measurement, which was not followed by any measurement.
A patient was considered a drop-out if a patient stopped participation due to withdrawal of consent, serious illness hindering participation and death; these reasons were registered separately (as also defined in 3.7).

5.5. Which baseline characteristics of participants will be presented?

The following baseline characteristics were presented:

- age;
- sex (female/male);
- body mass index (BMI);
- CTS complaints (unilateral/bilateral);
- dominant side more severely affected (yes/no);
- duration of CTS symptoms;
- CTS symptoms, in terms of a sensation of pins and needles, with or without pain, and numbness in median nerve innervated area of the hand (yes/no);
- CTS symptoms at night, which wake the patient (yes/no);
- worsening of CTS symptoms during certain hand or wrist movements (yes/no);
- neurological examination:
  - sensory disturbances;
  - paresis;
  - atrophy;
- secondary causes for CTS:
  - diabetes mellitus;
  - rheumatoid arthritis;
  - thyroid disease;
  - renal failure requiring dialysis;
  - anatomical abnormality at the carpal tunnel;
- ipsilateral CTS injections more than one year ago;
- CTS symptom severity (CTS-6 score);
- upper limb functioning (QuickDASH);
- health-related quality of life (EQ-5D-5L).

A mock-up of the baseline characteristics table is presented in the Appendix (Table 1) to this SAP.

5.6. How will the baseline characteristics be summarized?

Baseline characteristics were summarized for each treatment group using simple descriptive statistics. Continuous, approximately normally distributed variables (visually evaluated using histograms and Q-Q plots) were expressed as means and standard deviations; continuous, non-normally distributed and ordinal variables as medians and 25^{th}-75^{th} percentiles, and categorical variables as counts and proportions.

Section 6. Analysis.

6.1. How are the outcomes of this study defined?

The primary outcome was the proportion of participants recovered after 18 months follow-up. The proportion of participants recovered was measured using the six-item carpal tunnel symptoms scale (CTS-6 score; full scoring range six-30). Recovered was defined as a CTS-6 sum score of less than eight, which corresponds to 'no or mild' CTS symptoms.

Secondary outcomes were the following:

A) Time to recovery during 18 months follow-up;
first time point for outcome measurements after the last self-reported CTS intervention (*e.g.*, additional injection, surgery, splint) with a CTS-6 sum score of less than eight if this time point was followed by a CTS-6 sum score of less than eight at the next available time point or if this was the last available time point.

B) Proportion of participants recovered at different time points during 18 months follow-up;
the CTS-6 sum score was measured after six weeks and three, six, nine, 12, and 15 months follow-up. Recovered was defined as a CTS-6 sum score of less than eight if this time point was followed by a CTS-6 sum score of less than eight at the next available time point or if this was the last available time point.

C) Symptom severity at different time points during 18 months follow-up;
symptom severity was measured using the CTS-6 sum score after six weeks and three, six, nine, 12, 15, and 18 months follow-up.

D) Upper limb functioning after 18 months follow-up;
the functional status was measured using the QuickDASH (range zero-100).

E) Proportion of participants with scar or palm pain at different time points during 18 months follow-up;
severity of pain in scar/palm pain-related activity limitation was measured after six weeks and three, six, nine, 12, 15, and 18 months follow-up using the two-item palmar pain scale (range zero-100). The presence of scar or palmar pain was defined as a palmar pain score of more than zero, which corresponds to any pain and any limitation.

F) Participant's global perception of recovery after 18 months follow-up;
measured with a seven-point Likert-type item.

G) Participant's satisfaction after 18 months follow-up;
measured with a seven-point Likert-type item.

H) Health-related quality of life after 18 months follow-up;
measured with the EuroQol 5-level EQ-5D (EQ-5D-5L) after 18 months follow-up.

I) Additional treatments during 18 months follow-up;
additional undergone treatments were assessed after six weeks and three, six, nine, 12, 15, and 18 months follow-up.

J) Adverse events during 18 months follow-up;
defined as the nature and number of adverse events during follow-up. Included are adverse events of special interest (*e.g.*, wound infection, additional nerve damage, palmar pain) and adverse events that occurred in more than 5% of the patients in the surgery group or in the injection group. The presence of adverse events was assessed after six weeks and three, six, nine, 12, 15, and 18 months follow-up.

K) Cost-effectiveness and cost-utility from a societal perspective after 18 months follow-up;

the main outcome in the cost-effectiveness analysis was the costs per recovered patient (CTS-6 sum score of less than eight at 18 months). The main health outcome in the cost-utility analysis was the costs per number of Quality-adjusted life years (QALYs) gained. Patients' health status were assessed with the EQ-5D-5L at baseline and after 18 months follow-up.

6.2. Will any calculations or transformations be used to derive any outcome from the original data?

The primary outcome was the proportion of participants recovered at 18-months. The proportion of participants recovered was measured using the six-item carpal tunnel symptoms scale (CTS-6 score; full scoring range six-30). Recovered was defined as a CTS-6 sum score of less than eight. For the CTS-6 sum score the score for each of the six items (score range of the separate items one to five) were summed.

How missing values were handled for the primary outcome is described in section 6.7.

For symptom severity at different time points during 18 months follow-up (secondary outcome C) the CTS-6 sum score was used. Residuals in linear mixed model analyses were checked for approximate normality. If this was not the case a normalizing Box-Cox transformation (*e.g.*, square-root) was adopted on the CTS-6 sum scores.
For upper limb functioning after 18 months follow-up, the QuickDASH was used (secondary outcome D). The QuickDASH consists of 11 items. Each item has a score range from one to five. The outcome was calculated by using the following formula: ([(sum of *n* responses)/*n*] -1)(25) where *n* represents the number of completed items. This resulted in a score for the QuickDASH ranging from zero to 100. If less than 10 items were filled in, data were considered missing.

For scar or palm pain at different time points during 18 months follow-up (secondary outcome E), the two-item pain scale (mean score range zero to 100) was used, which consist of two items. For the item severity of pain, the following scores were possible: 0 referred to no pain, 20 to very mild pain, 40 to mild pain, 60 to moderate pain, 80 to severe pain, and 100 to very severe pain. For the item pain-related activity limitation, the following scores were possible: 0 referred to no limitation, 25 to a little limitations, 50 to moderate limitations, 75 to severe limitations, and 100 to very severe limitations. Severity of pain in scar and palm pain-related activity limitation was defined as a palmar pain score of more than zero, which corresponds to any pain and any limitation. Both items were analyzed separately.

QALYs were calculated by subtracting the health utility score at baseline from the health utility score at 18 months (secondary outcome H). The EQ-5D-5L contains five items: mobility, self-care, usual activities, pain/complaints, and mood (anxiety/depression). Each item has five response options: no problems, some problems, moderate problems, severe problems or extreme problems/unable to do.

Costs were considered from a societal perspective, consisting costs of health care resource use and subsequent costs, out-of-pocket expenses and costs reflecting loss of productivity at 18 months follow-up after randomization (secondary outcome K). Costs of resources used were calculated by multiplying the frequency of distinct resources used with their respective unit costs as appropriate.

6.3. What analysis method will be used and how will the treatment effects be presented?

Analysis method for primary outcome:
A difference in proportion of participants recovered between the surgery group and the injection group after 18 months was tested using Fisher's Exact Test. For the primary analysis, we considered the analysis a complete-case-analysis in case the percentage of participants with ascertainment of the primary endpoint did not exceed the predefined percentage of 20% of patients with drop-out or loss to follow-up. Effect size was expressed in a relative risk with its 95% CI.

Analysis method for secondary outcomes (formal statistical tests were not performed):

A) Time to recovery during 18 months follow-up;

Kaplan-Meier curves were generated and median times to recovery (with corresponding 95% CIs) were reported.

B) Proportion of participants recovered at different time points during 18 months follow-up;
were summarized as proportions (with 95% CI) in the surgery and injection group, and presented as the relative risk (with 95% CI).

C) Symptom severity at different time points during 18 months follow-up;
CTS-6 sum scores were analyzed (possibly after transformation) using a generalized linear mixed-effect model with treatment group as a fixed-effect and an appropriate random-effect structure (*e.g.*, patient-specific random intercept and random slope). Differences between the surgery and infection group were assessed on the basis of estimated mean differences (with 95% CI) for each time point during 18 months follow-up.

D) Upper limb functioning after 18 months follow-up;
were summarized as means (with 95% CI) in the surgery group and the injection group, and compared as mean difference (with 95% CI).

E) Scar or palm pain at different time points during 18 months follow-up;
severity scores were analyzed for both scale items separately and presented as relative risk (with 95% CI).

F) Participant's global perception of recovery after 18 months follow-up;
the perceived recovery scores were assessed as means (with 95% CI) in the surgery group and the injection group, and compared as mean difference (with 95% CI).

G) Participant's satisfaction after 18 months follow-up;
the perceived patient satisfaction scores were assessed as means (with 95% CI) in the surgery group and the injection group, and compared as mean difference (with 95% CI).

H) Health-related quality of life after 18 months follow-up;
the mean number of QALYs per patient were assessed as means (with 95% CI) in the surgery group and the injection group, and compared as mean difference using non-parametric bootstrapping procedure for 95% bias corrected and accelerated confidence intervals (BCa CIs).

I) Number of additional treatments during 18 months follow-up;
were summarized as proportions and presented with their corresponding 95% CIs.

J) Number of adverse events during 18 months follow-up;
were summarized as proportions and presented with their corresponding 95% CIs.

K) Cost-effectiveness and cost-utility from a societal perspective after 18 months follow-up; resource use was translated into healthcare costs, out-of-pocket expenses and productivity loss during 18 months follow-up and pooled by type of resource per treatment group (*i.e.*, surgery group and injection group) and summarized as means per patient with 95% BCa CI after non-parametric bootstrapping. Differences in mean (aggregated) costs are assessed using two-sample *t*-tests applying the previously mentioned non-parametric bootstrapping procedure for 95% BCa CIs. This is elaborated in the HEAP of the DISTRICTS.

6.4. Will any assumptions for statistical methods be checked?

Where appropriate, normality of data was explored by visual inspection of histograms and Normal Q-Q Plots. In addition, residuals in linear mixed-effect model analyses were checked for approximate normality. Furthermore, Kaplan-Meier curves were checked by visual inspection for non-crossing survival curves.

6.5. Will sensitivity analyses be performed?

We performed sensitivity analyses to evaluate the primary outcome (recovery after 18 months follow-up) to explore the robustness of the main analyses:

1. in all randomized patients with 18 months follow-up available, a logistic regression model was used, including the three stratification variables (*i.e.*, unilateral or bilateral CTS symptoms, secondary CTS due to a known underlying cause, and a history of previous ipsilateral CTS injections more than one year ago). This effect size was expressed in an adjusted odds ratio with corresponding 95% CI. In case of disbalance in baseline characteristics, we performed further multivariable analyses with inclusion of potentially confounding variables, such as age, gender, duration of symptoms, and severity of symptoms, to assess their effect on the primary outcome. This effect size was expressed in an adjusted odds ratio with corresponding 95% CI.
2. in all randomized patients after imputation of scores with missing data (to address the issue of missing data);
3. in the as treated population;
4. with an alternative definition of recovery: *i.e.*, a patient was classified as having recovered if he or she scored less than nine points on the total CTS-6 and fewer than three points on any individual item of the CTS-6. We performed the same unadjusted analysis as described for the primary outcome; this is the testing of a difference in proportion of participants recovered between the surgery group and the injection group after 18 months follow-up using Fisher's Exact Test (see section 6.3).

Regarding the economic evaluation, several sensitivity analyses were undertaken to explore uncertainties surrounding key parameters in the economic evaluation in concordance with observed uncertainties within the clinical analyses.

6.6. Will subgroup analyses be performed?

Prespecified subgroups were defined to evaluate the primary treatment effect (recovery after 18 months follow-up).

The following subgroups were evaluated:

- age (≤65y; >65 y);
- female *versus* male;
- Body Mass Index (≤25; >25-30; >30);
- CTS complaints (unilateral *versus* bilateral);
- history of previous ipsilateral CTS injections more than one year ago (yes or no);
- secondary CTS due to a known underlying cause (yes or no);
- dominant side more severely affected (yes or no);
- duration of CTS complaints (≤0.5 years; >0.5 years);
- severity of CTS complaints based on CTS-6 score (any separate item score ≤3 *versus* >3);
- atrophy (yes or no);
- severity of electrodiagnostic abnormalities (difference 4th finger comparative test ≤0.4 ms; >0.4-1.0 ms; >1.0 ms or absent median nerve sensory nerve action potential);
- severity of sonographic abnormalities (≤11 mm^2; >11-15 mm^2; >15 mm^2).

The subgroup analyses assessed the relative risks that the proportion of recovered patients in the surgery group would be higher after 18 months follow-up than in the injection group.

Regarding the economic evaluation, prespecified subgroup analyses were performed for relevant subgroups in line with the clinical analyses.

6.7. How will missing data be reported in the study reports and handled in the statistical analysis?

The numbers of missing CTS-6 scores and the proportion of missing CTS-6 scores for each visit and separate for each study group (*i.e.*, surgery group and injection group) were presented in a table.

Data imputation was only performed for the sensitivity analysis of the primary outcome; also see 6.5 - 2.
For participants with missing subitems of the CTS-6 after 18 months follow-up or without any CTS-6 measurement after 18 months follow-up, a prediction model was built for the missing values and was used to perform multiple sequential regression imputations, followed by multiple analyses and pooling of results, to obtain relative risks with 95% CI.

For the economic analysis, the appropriate method for dealing with missing data will depend on the proportion of missing data and likely mechanism of the missingness of data.

6.8. Will additional analyses on the primary or secondary outcomes be performed?

No additional analyses were performed on the primary or secondary outcomes.

6.9. How will harms be reported?

Adverse events and serious adverse events were reported in a table per patient by study group (*i.e.*, surgery group and injection group).

Adverse events and serious adverse events were reported in a table by actual treatment (*i.e.*, adverse effects were categorized according to the last preceding intervention).

6.10. Which statistical software will be used to carry out the statistical analyses?

All statistical analysis were performed in IBM SPSS Statistics for Windows, latest version (IBM Corp, Armonk, NY).

Section 7. References to literature, standard operating procedures and reporting guidelines.

7.1. Are non-standard statistical procedures to be used, which have not been described in sufficient depth in the previous sections?

Non-standard statistical procedures were not used.

7.2. What is the title, date and version number of the current data management plan?

The current data management plan has the title "Datamanagement ZonMw – DISTRICTS, version 1.0, dated 29-AUG-2017" and is stored in the trial master file.

7.3. What is the title, date and version number of the current data validation and derivation plan?

There is no data validation and derivation plan for the DISTRICTS study.

7.4. Where is the study master file stored?

The trial master file was stored at Amsterdam UMC, location AMC; neurology department; D2-139 and digitally on the Amsterdam UMC drive: G:\divd\neu\DISTRICTS\1 DISTRICTS Trial Master File.

7.5. Where are the syntax files for data extraction, manipulation and preparation and statistical analysis stored?

The syntax files for data extraction, manipulation and preparation and statistical analysis were stored digitally on the Amsterdam UMC drive: G:\divd\neu\DISTRICTS\1 DISTRICTS Trial Master File\17. Statistiek.

7.6. Which standard operating procedures will be adhered to when using and analyzing data from this study?

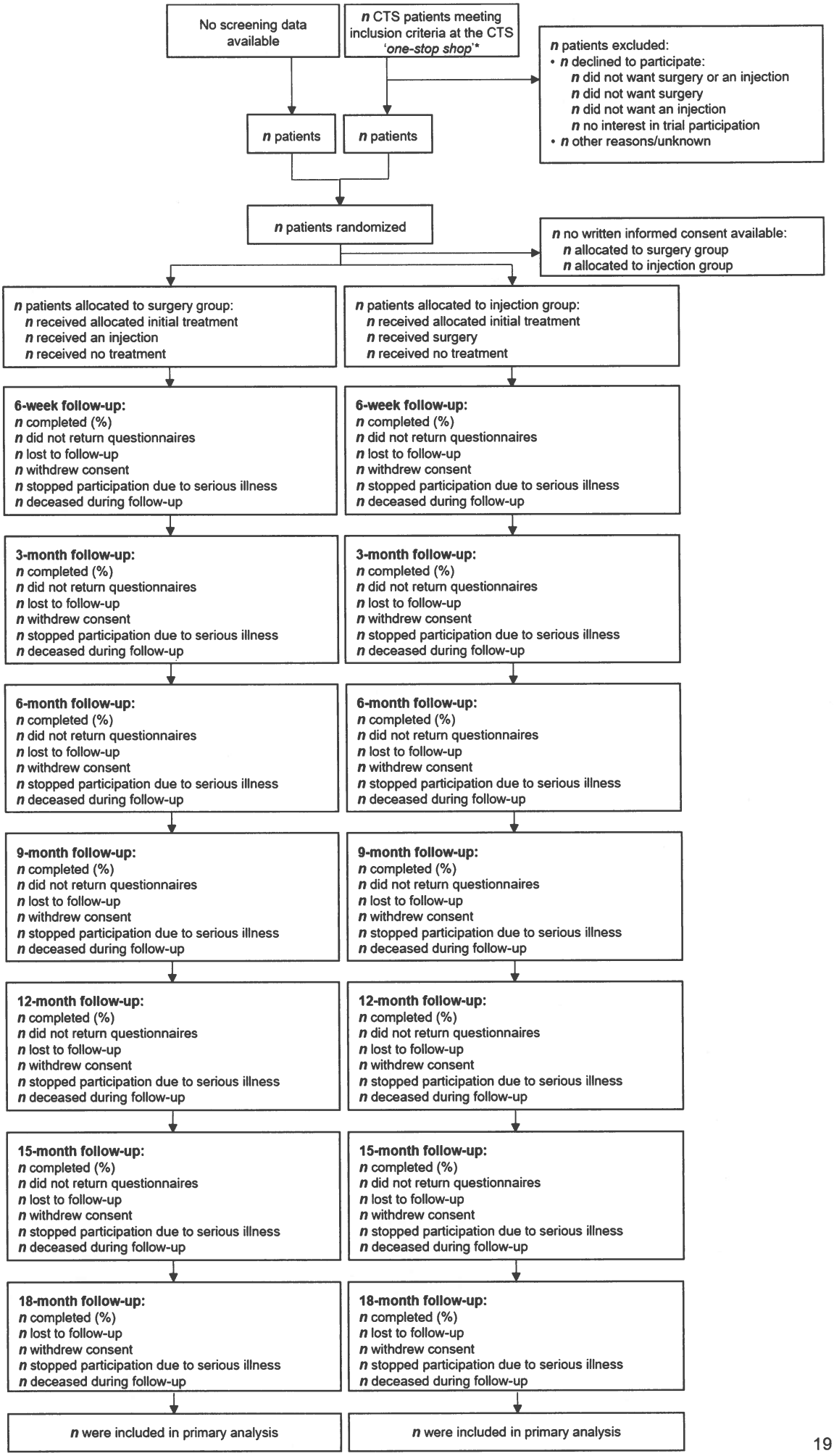
When using and analyzing data from the DISTRICTS, researchers will adhere to the standard operating procedure 001 Research data management.

7.7. Which reporting guidelines will be adhered to when reporting on this study?

When reporting the results of this randomized clinical trial, the researchers will adhere to the current CONSORT reporting guidelines.

Appendix. Additional Tables, Figures and Documents.

Figure 1. The flow chart of patients enrolled in the DISTRICTS trial.


No screening data available
n CTS patients meeting inclusion criteria at the CTS 'one-stop shop'*
n patients excluded:
• n declined to participate:
n did not want surgery or an injection
n did not want surgery
n did not want an injection
n no interest in trial participation
• n other reasons/unknown
n patients
n patients
n patients randomized
n no written informed consent available:
n allocated to surgery group
n allocated to injection group
n patients allocated to surgery group:
n received allocated initial treatment
n received an injection
n received no treatment
n patients allocated to injection group:
n received allocated initial treatment
n received surgery
n received no treatment
6-week follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
6-week follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
3-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
3-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
6-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
6-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
9-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
9-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
12-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
12-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
15-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
15-month follow-up:
n completed (%)
n did not return questionnaires
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
18-month follow-up:
n completed (%)
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
18-month follow-up:
n completed (%)
n lost to follow-up
n withdrew consent
n stopped participation due to serious illness
n deceased during follow-up
n were included in primary analysis
n were included in primary analysis

*Due to logistical complexity screening data was not completely registered. Eight recruiting hospitals registered CTS patients that visited the dedicated CTS outpatient clinic during their inclusion time period.

Table 1. Demographic and baseline clinical characteristics of patients randomized in the DISTRICTS trial.		
Characteristics	**Surgery group (*n*=...)**	**Injection group (*n*=..)**
Sex female, no. (%) male, no. (%)		
Age in years		
Body Mass Index		
CTS complaints unilateral, no. (%) bilateral, no. (%)		
Dominant side more severely affected yes, no. (%) no, no. (%)		
Duration of CTS symptoms in months		
CTS symptoms, in terms of a sensation of pins and needles, with or without pain, and numbness in median nerve innervated area of the hand yes, no. (%) no, no. (%)		
CTS symptoms at night, which wake the patient yes, no. (%) no, no. (%)		
Worsening of CTS symptoms during certain hand or wrist movements yes, no. (%) no, no. (%)		
Neurological examination sensory disturbances, no. (%) paresis, no. (%) atrophy, no. (%)		
Secondary causes for CTS diabetes mellitus, no. (%) rheumatoid arthritis, no. (%) thyroid disease, no. (%) renal failure requiring dialysis, no. (%) anatomical abnormality at the carpal tunnel*, no. (%)		
Ipsilateral CTS injections more than one year ago, no. (%)		
CTS symptom severity (CTS-6, range 6-30)		
Upper limb functioning (QuickDASH, range 0-100)		
Health-related quality of life (range 0-100)		

*Abnormality that may have induced changes in structures at the level of the carpal tunnel (*e.g.*, space-occupying lesion, status after trauma or surgery).