Statistical Analysis Plan for CHIP study: NSAID INFLUENCES ON FRAGMENT MIGRATION, PAIN AND FUNCTION AFTER COLLES FRACTURE (the CHIP study)

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NSAID INFLUENCES ON FRAGMENT MIGRATION, PAIN AND FUNCTION AFTER COLLES FRACTURE (CHIP) – trial statistical analysis plan

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1 Overview of analyses

This document contains the statistical analysis plan for the CHIP trial. The aim is to clarify analyses that will be performed during the trial, and thus avoid misleading inferences from post-hoc analyses. Therefore, this statistical analysis plan has been completed prior to the availability of any outcome data. This document describes the analyses to be performed. Separate manuscripts containing the trial outcomes will be prepared, with descriptive statistics and analyses following the structure set out in this document.

Regarding time-lines for analyses, the main time points was: recruitment of patients is finished in June 2015; and follow-up is finished in June 2016.

Input of data and preparation of the database containing data collected in the study will be conducted after the last visit of the last patient.

2 Background of the CHIP trial

One of the most used analgesics is NSAIDs (non-steroidal anti-inflammatory drugs). These are inflammation-reducing medications. However, inflammation is a very important part of the early stage of bone fracture healing. Indeed, many studies performed using animals have shown a clear tendency for delayed bone healing caused by the use of NSAIDs (Endo et al., 2005). However, this delay in healing was not apparent when NSAIDs were used over a short period of time (Krischak et al., 2007). It is also known that early intake of NSAIDs prevents ectopic ossification in patients receiving total hip prosthesis. However, cases of prosthetic loosening and instability after 10 years were almost exclusively observed in a group of patients who received NSAIDs postoperatively for 1–2 weeks (Persson et al., 2005). Nevertheless, few clinical studies show this trend in patients given NSAIDs over a short time (Williams, 2007). In this study, patients who have a fracture in the distal radius were included (Colles fracture). Many elderly patients sustain this type of fracture and may

subsequently have poor function in the injured wrist, especially if there is secondary dislocation of bone fragments (Solgaard, 1993).

Pain occurs in the early acute phase of a Colles fracture and thus raises indication for use of painkillers (Golec et al., 2015; Sorensen & Hansen, 2004). A common painkiller used in this situation is the NSAID Ibuprofen, which may be as effective as morphine in the treatment of acute fracture pain (Parish, 2014). However, it is unclear whether short-term treatment with Ibuprofen in the acute phase is beneficial for adult patients with Colles fractures, which would decrease the demand for morphine analgesics. This concern is especially important for patients with displaced Colles fractures, who need to be treated surgically and present greater pain before and after surgery (Davis & Ackroyd, 1988).

3 Consent

Written and signed informed consent was collected from all participants prior to inclusion in the study. The project is implemented in accordance with the requirements of Good Clinical Practice, and guidelines, requirements and allowance of the Danish National Drug Agency (Reg. Nr. 1253599), and the Danish Regional Ethic Committee (Reg. Nr. N-20100015). The study is also registered at the European Drug Agency (EudraCT number 2010-018543-34), and at the clinicaltrials.gov database.

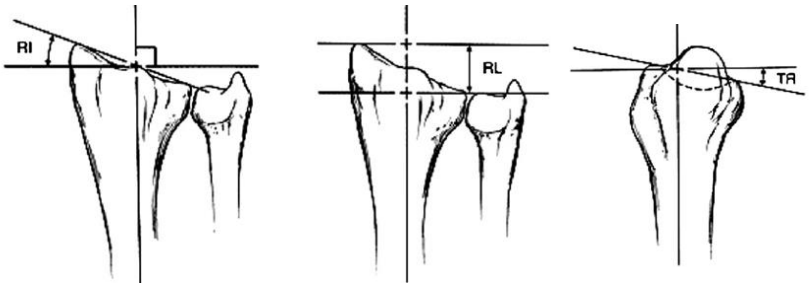
4 Outcomes

4.1 Primary outcome

The primary endpoint is the assessment of radiological secondary dislocation of radius volar tilt towards the dorsal side. Any migration larger in the NSAID treated group than in the control group will be an expression of instability and thus represent slower or absent healing.

We measured the radius' tilt at baseline before the initial reposition. We also measured the radius tilt immediately after the operation, and at one week, two weeks and six weeks after surgery. We expected the fractured bone fragments to migrate from the best position immediately after surgery, and towards a worse position later. The degree of dislocation regarding the radius tilt (measured in grades, 0 when in a neutral position, negative grades when there is volar tilt, and positive grades when there is dorsal tilt) is calculated as the difference between the result immediately after surgery and at the six week follow-up.

This difference is our primary outcome. The one and two week measurements will help to reveal secondary dislocation dynamics. All measurements will be performed by using X – ray EazyViz software package, allowing to determine this migration with a 1° and 1 mm accuracy. (*Picture 1*)



Picture 1 Radius inclination Radius length Radius tilt

4.2 Secondary outcomes

Several secondary outcomes were measured; these were shortening of the radius length, pain, use of escape analgesics, motion of the injured wrist, and everyday DASH, and are described as follows.

The first secondary radiological outcome was the assessment of the radiological shortening of the radius length according to ulna and inclination before the initial reposition, immediately after the operation, and at one week, two weeks and six weeks after surgery.

We expect fractured bone fragments to migrate from the best position immediately after surgery, and towards a worse position later. This secondary dislocation size, regarding the radius length (measured in millimeters) and inclination (measured in grades), is calculated as the difference between the result immediately after surgery and at the six week follow-up. This difference is the secondary radiological outcome. The one and two week measurements will help to reveal secondary dislocation dynamics.

Another secondary outcome was pain measured by VAS-score (Patients complete a pain diary in the first two postoperative weeks). We measured individual pain thresholds at baseline, which is calculated as the pain level difference (measured using the 10 point VAS scale) before and after reposition (with local anesthesia) at the Emergency Department (Kongsholm & Olerud, 1987; Hawker et al., 2011). First, we calculated the daily average of pain using the VAS scale (average of VAS points from three daily pain assessments – in the morning, midday and evening) for each patient in each group. We calculated the mean pain score for each of the following for each patient in each group: 1–3 days, 4–7 days and 8–14 days.

The use of escape analgesics – Tramadol 50 mg tablet – in treatment groups in the 1–3 day, 4–7 day and 8–14 day periods were also registered as secondary pain treatment endpoints.

The range of injured wrist joint motion was assessed in comparison to the non-injured wrist range of motion, and this constituted another secondary endpoint. We measured wrist movement from neutral position in three directions: extension and flexion; supination and pronation; and radial and ulnar deviation. The two components in each direction described three range of motion values: extension-flexion range, supination-pronation range, and deviation range. Given that the normal motion ranges may vary between individuals, we measured the baseline range of motion of the non-injured wrist joint. We also measured the

range of motion of the injured wrist at the six week, three month and one year follow-ups, and calculated the percent value of the normal range of motion. Percent value improvements from six weeks to one year will be calculated for each patient. This percent value of the normal range of motion at six weeks, three months and one year, and the value improvements are our secondary endpoints in this part of the study to determine mean differences between treatment groups.

The assessment of everyday DASH (disabilities of the arm, shoulder and hand) score is a quick and reliable assessment tool of normal daily function of patients (Westphal et al., 2002; Atroshi et al., 2000). A DASH questionnaire was completed by each patient together with their occupational therapist at the three month follow-up after surgery (rehabilitation begins postoperatively at six weeks) and the one year follow-up. The initial and final DASH scores and differences were registered for each patient.

5 Study design

Prospective, randomized, double-blind, controlled intervention trial**.** Patients were randomly divided into three groups:

Ibuprofen 600 mg three times a day for seven days – Group 1.

Ibuprofen 600 mg three times a day for the first three days, and a placebo tablet three times a day for the next four days – Group 2.

Placebo tablets only, three times a day for seven days – Group 3.

5.1 Study population

Patients, who fulfill the inclusion criteria, with acute unstable Colles fracture – Olders type III–IV – to be treated surgically, and stable Colles fracture – Olders type I–II – to be treated

conservatively, with plaster cast only. The inclusion period was from 01.06.2012 to 30.06.2015 in Aalborg University Hospital, Denmark.

5.2 Inclusion/exclusion criteria

Inclusion criteria. To be eligible for the study, subjects must fulfill the following criteria:

1. Age: 40–85 years.
2. Written acceptance after informed consent.
3. Colles fracture, Olders type III – IV, with indication for surgical treatment (poor result of reposition and/or instability).

Exclusion criteria. To be eligible for this study, subjects must not meet any of the following criteria:

1. Age – younger than 40, older than 85 years.
2. Systematic treatment with NSAIDs.
3. Previous fracture at the actual wrist.
4. Lack of mental and physical capacity to follow study instructions.
5. Medical contraindications to NSAID use.
6. Pregnancy.

Secondary dislocation of fracture classifies as drop-out and patients must leave the study.

5.3 Sample size

Sample size calculation is based on the primary outcome of our study – changes in radius tilt. The sample size has been calculated to test our null hypothesis that treatment with NSAIDs is inferior to placebo. In the NSAID group, the estimate of participants meeting criteria for the primary endpoint is based on a 1 SD incidence of additional dorsal tilt. We will set a non-inferiority margin of 1 SD for this study. Thus, the primary null hypothesis for this trial is $H0$:$\mu NSAID$ - μplacebo > 1 SD (inferiority), where $\mu NSAID$ and μplacebo are the

means of the primary outcome occurring in the NSAID arm and the placebo arm, respectively. The alternative hypothesis on which the sample size is based is $H1$:$\mu NSAID$ - $\mu placebo \leq 1$ SD. The power for this trial will be set to 90 %; therefore, to have an 80% probability of rejecting $H0$ when $H1$ is true, using a one-sided, 0.05 level test, we will require a total of 78 participants (3 equal groups of 26). To allow for a combined 20% drop-out and loss to follow-up, we intend to recruit 96 (*i.e.* 78/0.8) participants in total: three groups with 32 patients in each.

We used the mean pain score for each of the three groups over fourteen days for our sample size calculation for the secondary outcome pain. With a significance level of 0.05, a strength of 95%, a standard deviation of 1.41 and the potential to detect a difference of 1.5 VAS points between group pain score averages, 23 patients are needed in each group. Thus, the sample size planned for the primary outcome is also appropriate for this secondary outcome. To detect a 15% difference in extension – flexion range improvements – between treatment groups with a significance level of 0.05, a strength of 95%, and a standard deviation of 14.5, we need 25 subjects in each of the three treatment groups. Therefore, the planned sample size is also appropriate for the secondary outcome, range of motion.

5.4 Randomization and blinding

The hospital's Pharmaceutical Department performed block randomization: five blocks with nine patients in each, eight blocks with six patients in each and one block with three patients. Painkillers, according to the randomization, was supplied in packets. The patient, one single surgeon, the data manager and statistician were all blinded. Only the project pharmacist had access to the list of contents of each packet.

6 Statistical plan for main outcome paper

Statistical analyses will be performed using R program (the same program as we used for

sample size calculation).

6.1 Consort diagram

A detailed CONSORT diagram, describing patient flow with exclusions and total numbers randomized to each treatment, will be produced. This diagram will include all randomized patients.

6.2 Descriptive statistics

Baseline variables will be displayed in tables of summary statistics: n (non-missing sample size), mean, standard deviation, median, quartiles, minimum, and maximum.; these will include initial radius inclination, length, angulation, threshold of pain, and normal range of motion. The number of missing observations will also be reported.

6.3 Primary outcome analyses

Primary outcome is a nummerical quantitative data, therefore a parametric significance test will be (if possible) our first choise. Data from each sample will be checked for normal distribution by drawing a boxplot, frequency histogram, and a Q-Q plot to determine normal distributions. In case of doubt, a Shapiro-Wilk test for normality will be performed. To test for homoscedasticity of treatment groups, Bartlett's test will be performed

In case of normal distribution and homoscedasticity in all samples, we will use Student's *t*-test with Dunn-Šidák correction, $\alpha = 1 - (1 - 0.05)^{1/k}$, (where k is the number of hypotheses tested) to detect potential significant differences between group mean changes in radius tilt immediately following surgery and at the six week follow-up. In case of non-equal variances, but normal distribution, an unequal variance test (Welsh's t-test) with Dunn-Šidák correction will be performed.

If data are not normally distributed, we will use a Kruskal-Wallis non-parametric significance test.

6.4 Secondary endpoints

Radius inclination and tilt are a nummerical quantitative data, therefore a parametric significance test will be (if possible) our first choise. Data from each sample will be checked for normal distribution by drawing a boxplot, frequency histogram, and Q-Q plot to determine a normal distribution. In case of doubt, Shapiro-Wilk test for normality will be performed. To test for homoscedasticity of treatment groups, Bartlett's test will be performed

In case of normal distribution and homoscedasticity in all samples, we will use Student's *t*-test with Dunn-Šidák correction, $\alpha = 1 - (1 - 0.05)^{1/k}$, (where k is the number of hypotheses tested) to detect potential significant differences between group mean changes in radius inclination and length measured immediately following surgery and at the six week follow-up.

Changes of mean pain score for each of the three groups in the first 1–3 days, 4–7 days and 8–14 days, and and value improvements and DASH score results from 3 months to 1 year are based on qualitative data from VAS and DASH questinaries. Therefore, a non parametric Kruskal-Wallis significance test will be used.

Changes of percent value of normal range of motion at six weeks, three months and one year of follow-up, average use of escape Tradolan for each of the three groups in the first 1–3 days, 4–7 days and 8–14 days ar nummerical quantitative data. Parametric significance test will therefore be our first choise, if possible. In case of normal distribution and homoscedasticity in all samples, we will use Student's *t*-test with Dunn-Šidák correction, $\alpha = 1 - (1 - 0.05)^{1/k}$, (where k is the number of hypotheses tested) to detect potential significant differences between group mean differences. In case of non-equal variances, but normal

distribution, an unequal variance test (Welsh's t-test) with Dunn-Šidák correction will be performed. If data are not normally distributed, we will use a Kruskal-Wallis non-parametric significance test.

6.5 Subgroup analyses

We are concerned about potential confounders. Regarding the primary outcome, bone dislocation levels before treatment (and thus, instability) may influence secondary dislocation.

As for secondary outcome pain, the individual threshold of the pain may influence each patient's pain experience during the treatment with the study drugs and later in the trial (Sorensen & Hansen, 2004).

The secondary outcome range of motion may be influenced by whether the dominating or non-dominating hand is injured. It is possible that rehabilitation of the dominating hand is easier, and that the range of motion improves faster.

We will therefore perform a correlation analysis 1) between baseline dislocation measurement as the independent variable and secondary dislocation level as the dependent variable.

Furthermore, a correlation analysis will be performed 2) between threshold pain (pain score between reposition-subtracted pain score after local anesthesia, reposition, and cast immobilization) as the independent variable and individual patients' total sum of pain score for 14 days as the dependent variable.

In correlation analysis, we test the significance of the correlation coefficient at the $P<0.05$ level.

For analysis 3), we will determine whether the range of motion improvement and DASH score are influenced by hand domination, and we will do this as follows: each of the three treatment groups is divided into two subgroups – dominating hand and non-dominating hand. We will calculate the mean percent value of normal range of motion of injured wrists in each subgroup at six weeks and one year by using the following formulae:

Mean $\%_{6\ weeks}$ = (% extension and $flexion_{6\ weeks}$ + % supination and $pronation_{6\ weeks}$ + % $deviation_{6\ weeks}$)/3

Mean $\%_{1\ year}$ = (% extension and $flexion_{1\ year}$ + % supination and $pronation_{1\ year}$ + % $deviation_{1\ year}$)/3

Mean % improvement = mean $\%_{1\ year}$ - mean $\%_{6\ weeks}$

Results will be tested for normal distribution and equal variances by using frequency histograms, boxplots, Q-Q plots, Shapiro-Wilk test (for normal distribution) and Bartlett's test (for equal variances). In case of normal distribution and equal variances, a *t*-test, with significance level 0.05 and power 80%, will be used to test differences between dominating and non-dominating divisions.

In case of non-normal distribution, a Mann-Whitney U test will be performed. Results will be displayed in the table:

	Dominating arm	**Not dominating arm**	**Diff. (dominating - non-dominating)**	**Statistics**
Range % start				
Range % finish				
Range % improvement				
DASH 3 months				
DASH 1 year				
Mean DASH				
DASH fall				

7 Handling of missing data

The primary outcome analysis may be subject to missing data due to poor X-ray quality or lack of proper projection, and forgotten records in patients' pain diaries.

Missing data that occurs will be multiply imputed in the primary analysis to increase precision of the estimates and to avoid potential biases. All imputations will be examined to ensure sensible values are being generated. Imputation models will contain baseline variables and outcome variables.

8 Implementation of analysis plan

This statistical analysis plan will be used as a work description for the statistician performing the analyses. All analyses will be performed by the same statistician and none of the investigators involved in this trial will perform any of the statistical analyses.

The implementation of the SAP will be as follows:

1. A 'data collection form' will be outlined in a collaboration between the database managing principal investigator (Marius Aliuskevicius) and statistician.
2. The database manager will code each treatment arm into 'Group 1', 'Group 2' and 'Group 3', thus leaving all others blinded from treatment during the analyses.
3. Blinded data will be delivered to the statistician according to the 'data collection form'.
4. Primary, secondary and exploratory endpoint analyses will be made blinded from treatment.
5. Results will be presented to the writing committee of the trial (identical to the study chair in this SAP), where any uncertainties will be clarified, and blinded

interpretations of the primary endpoint results will be conducted prior to unblinding of data.

9 Adverse events

Adverse events are reported throughout the trial, and tabulations of all reported adverse events will be provided, subdivided by treatment group.

Special focus will be awarded to several adverse events as evaluated by the sponsor-investigator.

10 References

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