Statistical analysis plan for Inpatient versus Outpatient Care after Anterior Cervical Decompression and Fusion: A prospective randomised non-inferiority trial

NCT03979443

August 16th 2022

We, the Blinded Data Interpretation Committee of the FACADE trial, have reached a consensus on how to carry out the blinded data interpretation (BDI). The document coined “Minutes for FACADE blinded data interpretation” (next page) outlines the execution of the blinded data interpretation for the FACADE trial.

Statistical analysis will be carried out by the trial statistician without any involvement from members of the Blinded Data Interpretation Committee or other FACADE investigators, as outlined below. The central study coordinator will code the trial data (two treatment arms) as ‘Group A’ and ‘Group B’ before handing the data over to the statistician. This will help ensure that the statistical analyses will be performed blind to the treatment allocation.

To reduce risk of interpretation bias, blinded results from the ITT analysis (Group A vs. Group B) will be presented to the Blinded Data Interpretation Committee. The Blinded Data Interpretation Committee will then contemplate on two alternative written interpretations, one where group A is the Inpatient care strategy and one where Group A is the Outpatient care strategy. Only after the Blinded Data Interpretation Committee has reached a consensus on the proper interpretation of the findings, the central study coordinator will unblind the treatment group allocation.

Also, as Drs. Lönnrot and Satopää were involved in the clinical care of the patients, they will recuse themselves from making any interpretations but are to take part in the blinded data interpretation meeting to answer potential questions regarding the execution of the trial.

Finally, the undersigned (members of the FACADE Blinded Data Interpretation Committee) agree that the minutes of the upcoming blinded data interpretation meeting will be emailed to an independent scientist for external review (comments/requests for clarification) before the final manuscript is submitted.

FACADE Blinded Data Interpretation Committee August 16, 2022

Teppo Järvinen, MD, PhD (Chair, co-PI of the FACADE)

Simo Taimela

Simo Taimela, MD, PhD (Co-Chair)

Tomasz Czuba

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Tomasz Czuba, Trial statistician

Kimmo Lönnrot, MD, PhD (FACADE PI)

Minutes of the FACADE Blinded Data Interpretation meeting for Manuscript:

Inpatient versus Outpatient Care after Anterior Cervical Decompression and Fusion: A prospective randomised non-inferiority trial

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Background and trial objectives

During the past decade, cervical spine procedures have increasingly been performed on an outpatient basis and retrospective database analyses have shown this to be feasible and safe. However, to our knowledge, no randomized controlled trial exists to compare the safety and efficacy/effectiveness of outpatient vs. inpatient care in patients undergoing anterior cervical decompression and fusion (ACDF) procedure.

We designed a randomized controlled study comparing outpatient and inpatient care in patients undergoing ACDF, with a primary objective to assess whether outpatient care is non-inferior to inpatient care with regards to the patients' perception of symptom relief (assessed by NDI, our primary efficacy outcome).

Methods

Trial design and oversight

In this three-center, stratified, block-randomized trial we randomized 104 patients after ACDF procedure to two treatment groups in a 1:1 ratio: A strategy of early (6-8 hours after procedure) discharge (Outpatient group) or a strategy of staying under hospital surveillance overnight (Inpatient group).

The full study protocol of the FACADE study has been published[1]. The participating centers and study group are listed in the Supplementary Appendix. The trial was designed and conducted by the FACADE investigators and the analyses were completed at the coordinating center. The trial protocol was approved by ethical review at the institutional review board of the Helsinki and Uusimaa Hospital District on June 6, 2019 (1540/2019) and duly registered at ClinicalTrials.gov (NCT03979443: https://clinicaltrials.gov/ct2/show/NCT03979443). All participants provided written informed consent. The trial was monitored by Clinical Research Unit of the Helsinki University Hospital (HYKSIN Institute), Helsinki, Finland. The writing committee of the FACADE trial vouch for the accuracy and completeness of the data, the fidelity of the trial to the protocol, and the complete reporting of adverse events. There was no industry involvement in the trial.

The FACADE trial was launched in the coordinating center (Helsinki) on June 12, 2019. The next trial center (Turku University Hospital) joined the trial on January 16, 2020 and the third (Oulu University Hospital) on January 23, 2020. Both Helsinki and Turku retained in the trial until patient recruitment was completed (February 12, 2021). However, due to Covid-19 situation, Oulu was able participate trial only until May 30, 2020.

Participants

During the recruitment period of the trial, we screened all patients suffering from radiating arm pain referred to the study centers for trial eligibility (n=782). After being fully informed of the trial protocol, 104 eligible patients willing to participate (written informed consent) were randomized.

Randomization and Blinding

After the surgery, all patients were taken to the recovery room for 2 to 3 hours for an immediate postoperative observation. When we had confirmed that the patients were fully conscious and co-operative, and immediate postoperative complications were

ruled out using a postoperative checklist, patients' final eligibility was confirmed. A member of the FACADE study group then randomized the patients either to the Outpatient group (discharge within the same day) or the Inpatient group (overnight surveillance at the hospital). The randomisation was a built-in property in the online electronic case report form (eCRF) system used in the trial (Granitics Ltd., Espoo, Finland). To minimise the risk of predicting the treatment assignment of the next eligible patient (to ensure concealment), we performed randomisation with variable block size (block size known only to the statistician with no involvement in the clinical care of the participants in the trial).

Study Interventions

Outpatient group
A ward nurse evaluated all patients allocated to the Outpatient group approximately 6-8 hours after surgery using a standardised FACADE discharge checklist. If the patient fulfilled all discharge criteria, he/she was instructed on how to deal with any concerns and was discharged. At discharge, we documented the time elapsed from operation and provided the patients with prescriptions to manage postoperative pain and an absence from work medical certificate for the first postoperative week.

Inpatient group
Patients allocated to inpatient care were kept in the hospital for surveillance overnight. A neurosurgeon on duty assessed whether patients were fit to be discharged on the 1st postoperative day. Identically to the Outpatient group, we documented the time elapsed from operation at discharge. We also provided the patients with prescriptions for postoperative pain management and an absence from work medical certificate for the first postoperative week.

Outcome measures

Primary (efficacy) outcome measure
Our primary outcome measure was the Neck Disability Index (NDI; scale 0 to 100, with higher scores indicating worse outcomes and more symptoms), a validated, neck-specific, patient reported measure of pain-related dysfunction[2,3]. We used a validated Finnish version of the NDI[4]. The primary assessment time point was six months. We also gathered the NDI at one and three months postoperatively, but this data was only intended to illustrate the trajectory of the treatment responses (Table 2). Our pre-defined threshold for minimal important difference (MID) of the primary outcome (NDI) was set at 17.3% (improvement from the baseline value), based on previous literature[5].

Details of all other outcome measures can be found in the protocol and the Supplementary Appendix.

Sample size

Originally, the trial was powered to detect an MID in the NDI score between the two study groups. We set the MID for NDI (17.3%) as our margin of non-inferiority Δ based on the results by Parker et al.[5] Assuming no difference between treatment arms (ε = 0 in NDI score improvements), equal sample sizes (x=1, the SD 23%), a margin of non-inferiority Δ of 17.3%, one-sided 2.5% statistical significance criteria (z_α = 1.96) and 90% statistical power (z_β =1,28), the required sample size was 44 patients per study

group. When also taking a dropout rate of 15% into account, the group size increased to 52 patients. Accordingly, we set the recruitment target at 104 patients.

However, while our statistician (TC) was preparing the plan for blinded data interpretation, he noticed that we had erroneously chosen an incorrect value for SD (in the study by Parker et al.[5], the mean improvement for NDI was 23.2 while the standard deviation (SD) was 19.7%). Keeping all other parameters constant, he recalculated the required sample size: The recruitment target turned out 29 subjects per group (without adjusting for dropouts) and 35 subjects per group (after adjusting for a 15% dropout rate), respectively.

Statistical analysis

The trial is primarily designed to ascertain whether outpatient care is non-inferior to inpatient care, at 6 months after surgery, with NDI as the primary outcome. Only one primary analysis will be used to assess non-inferiority. At the 6-month time point, non-inferiority can be claimed if the lower limit of the CI (based on difference in means in the NDI) is greater than the MID in the primary comparison.

According to the CONSORT (Consolidated Standards of Reporting Trials) statement for non-inferiority and equivalence trials[6], secondary outcomes can be managed using either a superiority or equivalence framework. In our trial, all secondary outcomes will be assessed with an equivalence hypothesis, but since our trial is not necessarily powered for these comparisons, and to avoid issues with multiplicity, we consider them exploratory or hypothesis-generating.

We will follow primarily intention-to-treat (ITT) principle in all our analyses. In the ITT analyses, the participants are included as randomised. Per-protocol and on-treatment analyses will also be used to avoid falsely claiming non-inferiority. Summary statistics will be given as mean (with SD) for continuous variables and as frequencies (with %) for categorical variables. Repeated measures mixed model (RMMM) analysis will be used for all continuous variables (both primary and secondary outcomes) where regression coefficients are allowed to differ between study subjects. Statistical significance is set to two-sided 5% level. The RMMM analysis allows the use of all available observations in the data set, so the full data set (data set without multiple imputation) will be used in the analysis. Logistic regression will be used to assess categorical variables. STATA (Statistics/Data analysis, SE v15.1, StataCorp LLC, 4905 Lakeway Drive, College Station, Texas 77845 USA) will be used for analyses.

Blinded data interpretation

The data will be interpreted according to a blinded data interpretation scheme we have published and described in detail previously.[5] In brief, FACADE statistician (TC) will carry out the statistical analyses, blinded to the group assignment, and presents the data as Group A and Group B. The FACADE Blinded Data Interpretation committee will then contemplate on the blinded results until a consensus on the interpretation is reached. Once the Blinded Data Interpretation committee reaches a consensus, the data will be unblinded and no changes are made to the interpretation of the results.

In keeping with the pre-defined interpretation plan for the FACADE trial, we will adhere to the following plan in presenting and interpreting the data (presented as Group A and Group B to preserve blinding) at the BDI meeting:

1. Analysis on efficacy (primary, non-inferiority analysis): Is outpatient care non-inferior to inpatient care after anterior cervical decompression and fusion?

- Table 1. Baseline characteristics.
- Table 2. Primary outcome (NDI) at the primary outcome assessment time point (6 mo).
- Figures 2 and 3: Two possible scenarios – Group A vs. Group B and Group B vs. Group A.

Based on this data, we will make an initial (blinded) interpretation on non-inferiority.

2. Treatment-related adverse consequences of both treatment strategies (Safety concerns)

Before finalising our interpretation on clinical relevance of our findings, we will assess the safety of the two treatment arms:

Table 3. Complications, adverse events, re-admissions to hospital

According to our own data on the safety of the ACDF procedure (overall complications rates < 10%), this analysis will likely not be powered to materially change our main conclusion, particularly with regards to the most feared complication (neck haematoma), which has a reported incidence of <1%.

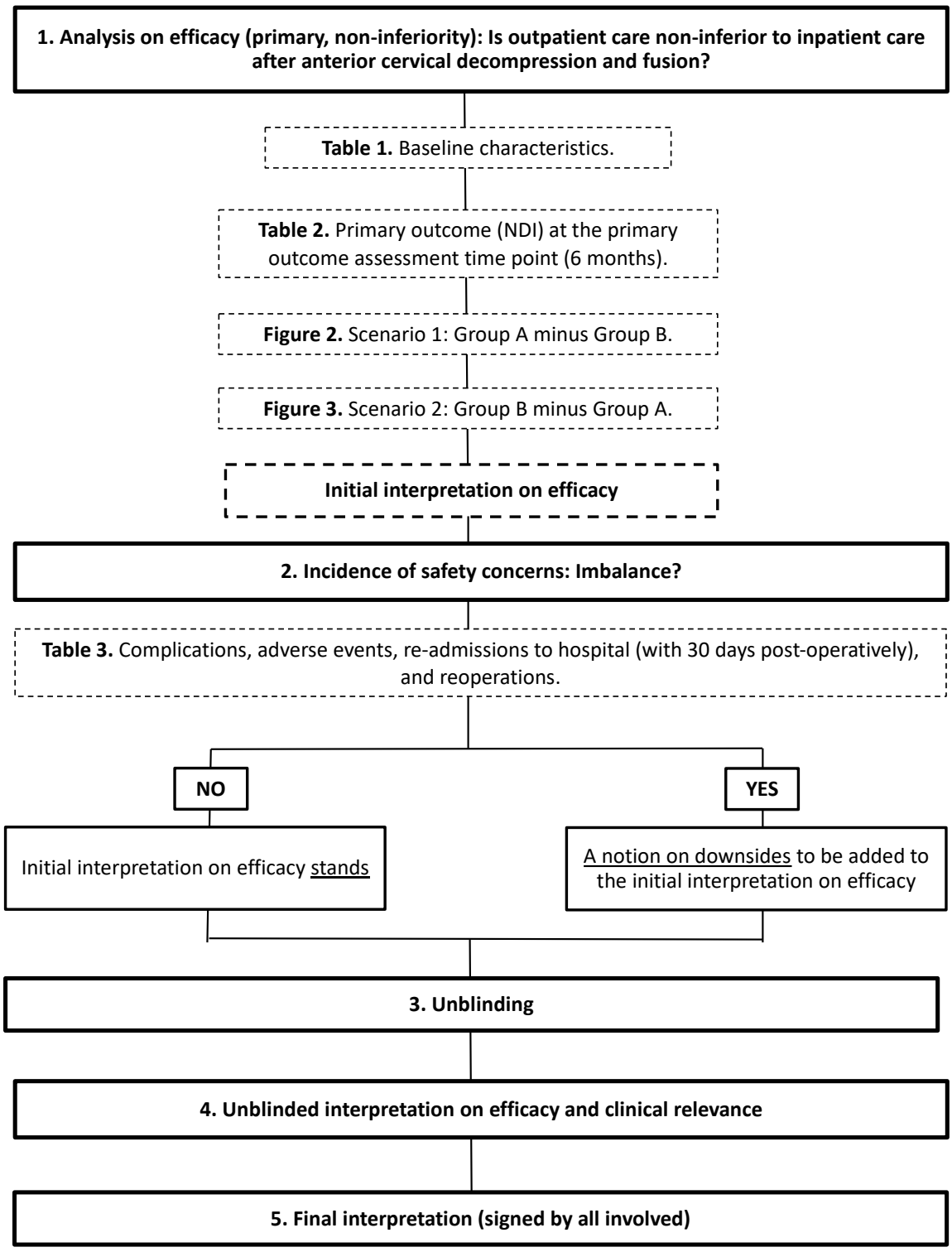
Having said this, to be completely transparent and inclusive about the possible effect of adverse consequences on the clinical relevance (our interpretation) of the trial findings, we commit to assessing the overall rate (incidence) of safety concerns before final interpretation is made as follows:

If we detect > 10% difference in the overall incidence of serious adverse events between the two group (treatment strategies), we will add the following notion in our conclusion:

"*However, there was a noteworthy imbalance in the incidence of safety concerns in the two treatment strategies (higher/lower rate in Group A) and this should be considered when interpreting the trial findings.*"

As noted, the analysis on the downsides of the two treatments will not change our assessment **on efficacy**, rather modify our interpretation on the clinical relevance of the trial.

The sequence of events to take place in the upcoming "blinded data interpretation meeting" is outlined in the flow chart below:


1. Analysis on efficacy (primary, non-inferiority): Is outpatient care non-inferior to inpatient care after anterior cervical decompression and fusion?
Table 1. Baseline characteristics.
Table 2. Primary outcome (NDI) at the primary outcome assessment time point (6 months).
Figure 2. Scenario 1: Group A minus Group B.
Figure 3. Scenario 2: Group B minus Group A.
Initial interpretation on efficacy
2. Incidence of safety concerns: Imbalance?
Table 3. Complications, adverse events, re-admissions to hospital (with 30 days post-operatively), and reoperations.
NO
YES
Initial interpretation on efficacy stands
A notion on downsides to be added to the initial interpretation on efficacy
3. Unblinding
4. Unblinded interpretation on efficacy and clinical relevance
5. Final interpretation (signed by all involved)

1. Analysis on efficacy (primary, non-inferiority): Is outpatient care non-inferior to inpatient care after anterior cervical decompression and fusion?

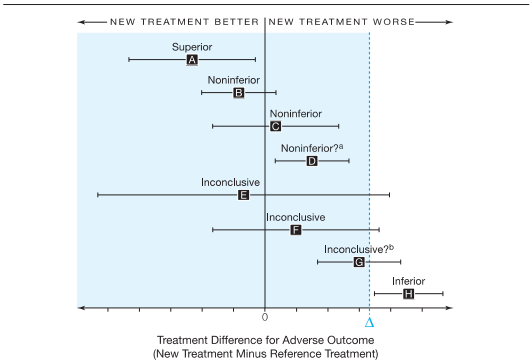
Table 1. Baseline characteristics.

	Group A		Group B	
		Mean ± SD		Mean ± SD
Age (years), mean (SD)				
Gender (female), n				
Dominant hand affected, n				
Work Ability Score (WAS)				
Physically demanding job: “heavy labor”, n				
Patient’s own estimate of job demands: “heavy” n				
Ability to work normally irrespective of the symptoms? n				
Participation in leisure time activities irrespective of the symptoms? n				
Duration of symptoms (days), mean (SD)				
Preoperative sick leave (days)				
Prior treatments (Physiotherapy) n				
NSAID Pain medication, n				
Opioid pain medication, n				
Neuropathic pain medication, n				
Neck Disability Index (NDI) (scale: 0 to 100), mean (SD)				
Neck pain at rest (NRS scale: 0 to 10), mean (SD)				
Arm pain at rest (NRS scale: 0 to 10), mean (SD)				
EuroQol-5 dimensions-5 levels Time Trade-Off index score (0 to 1)				
EuroQol-5 dimensions-5 levels Health Visual Analogue Scale (0 to 100)				

Table 2. Primary outcome at the primary outcome assessment time point (6 months).

Table 2. Primary outcome at six months					
	Group A		**Group B**		**Difference (95% CI)**
		Mean ± SE		Mean ± SE	
Primary efficacy outcome					
Neck Disability Index (Scale: 0 to 100)		?? ± ??		?? ± ??	?? ± ??
***Means and standard errors are derived from a general linear repeated measures model analysis.** **Abbreviations: CI: Confidence Interval; SE: Standard Error**					

Our judgment on the efficacy (non-inferiority) will be based on the location of the whole CI in relation to Δ (non-inferiority margin), as outlined by Piaggio et al[6].



Error bars indicate 2-sided 95% CIs. The blue dashed line at x=Δ indicates the noninferiority margin; the blue tinted region to the left of x=Δ indicates the zone of inferiority. A, If the CI lies wholly to the left of zero, the new treatment is superior. B and C, If the CI lies to the left of Δ and includes zero, the new treatment is non-inferior but not shown to be superior. D, If the CI lies wholly to the left of Δ and wholly to the right of zero, the new treatment is noninferior in the sense already defined but also inferior in the sense that a null treatment difference is excluded. This puzzling circumstance is rare, because it requires a very large sample size. It also can result from a noninferiority margin that is too wide. E and F, If the CI includes Δ and zero, the difference is nonsignificant but the result regarding noninferiority is inconclusive. G, If the CI includes Δ and is wholly to the right of zero, the difference is statistically significant but the result is inconclusive regarding possible inferiority of magnitude Δ or worse. H, If the CI is wholly above Δ, the new treatment is inferior.
[a]This CI indicates noninferiority in the sense that it does not include Δ, but the new treatment is significantly worse than the standard. Such a result is unlikely because it would require a very large sample size.
[b]This CI is inconclusive in that it is still plausible that the true treatment difference is less than Δ, but the new treatment is significantly worse than the standard. Adapted from Piaggio et al.[6]

As we will not have knowledge of treatment group assignment (whether Group A or Group B is our "new treatment": here, Outpatient care), and to preserve our blinding, we have deemed it necessary to take both scenarios under consideration, as follows:

- We will calculate the treatment group difference assuming first that Group A is the "new treatment" and then that Group B is the "new treatment" (Scenario 1 and Scenario 2).
- We will plot the resulting point estimate with error bars (95% Cis) into two separate graphs.
- We will interpret both graphs (**Figures 2** and **3**).

Figure 2. Scenario 1: Group A minus Group B.

(EXAMPLE GRAPH BELOW, to be replaced by the actual graph of the FACADE trial data).

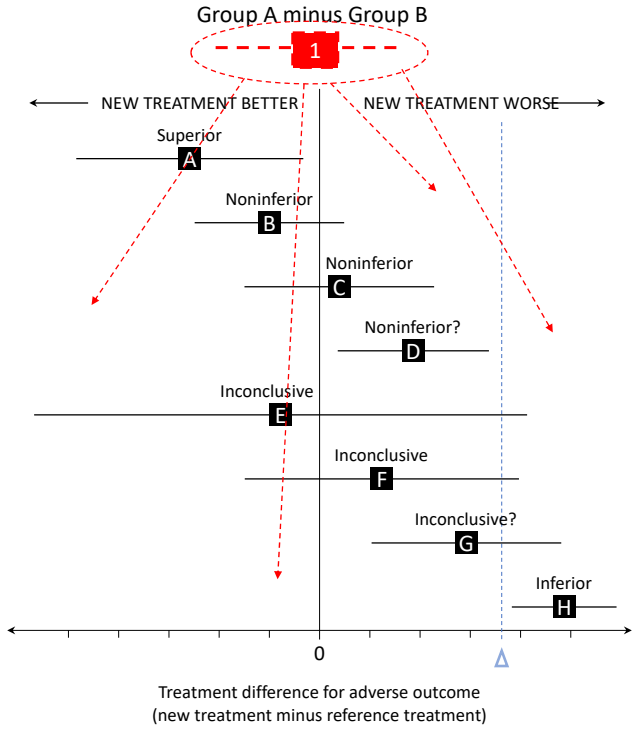
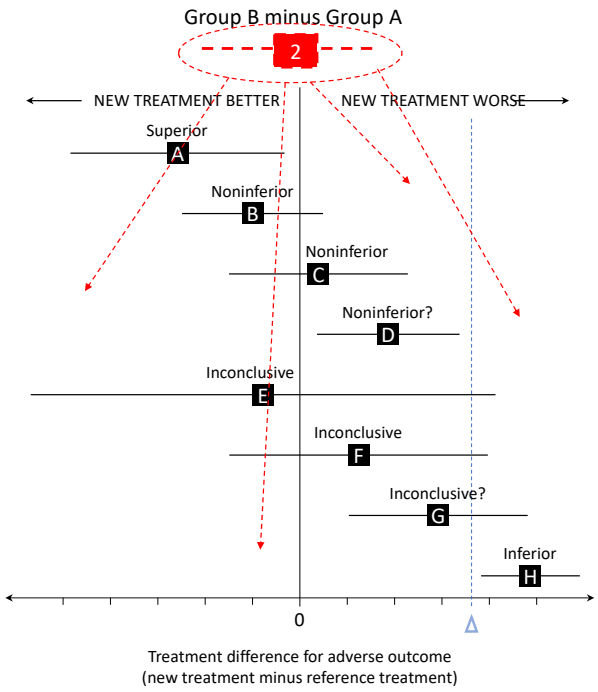


Figure 3. Scenario 2: Group B minus Group A.

(EXAMPLE GRAPH BELOW, to be replaced by the actual graph of the FACADE trial data).



Initial interpretation:

Based on the location of the whole CI in relation to Δ (non-inferiority margin), our initial interpretation on the non-inferiority of Outpatient care (vs. Inpatient care), is as follows:

Scenario 1 (Figure 2) [incorrect options to be removed]

Group A is [superior A / non-inferior B to D / inferior H] to Group B after anterior cervical decompression and fusion.

OR

Our results are inconclusive [E to G] regarding the non-inferiority of the two groups after anterior cervical decompression and fusion.

Scenario 2 (Figure 3) [incorrect options to be removed]

Group B is [superior A / non-inferior B to D / inferior H] to Group A after anterior cervical decompression and fusion.

OR

Our results are inconclusive [E to G] regarding the non-inferiority of the two groups after anterior cervical decompression and fusion.

2. Safety concerns

Table 3. Complications, adverse events, re-admissions to hospital (with 30 days post-operatively), and reoperations.

	Group A	Group B
Acute perioperative complications	n	n
Serious Adverse Events (SAE)	Below % will represent % of SAE/MAE/Cause of reop in group A not % of total N	Below % will represent % of SAE in group B not % of total N
Cardiovascular event	n (%)	n (%)
Pulmonary embolus	n (%)	n (%)
Deep venous thrombosis in leg	n (%)	n (%)
Subcutaneus neck haematoma	n (%)	n (%)
Systemic infection	n (%)	n (%)
Postoperative hemi- or tetraplegia	n (%)	n (%)
Persistent dysphonia at 6 months	n (%)	n (%)
Persistent dysphagia at 6 months	n (%)	n (%)
Death	n (%)	n (%)
Other	n (%)	n (%)
Minor Adverse Events (MAE)		
Wound infection	n (%)	n (%)
Motor deficit (new)	n (%)	n (%)
Persistent symptoms	n (%)	n (%)
Dyspnea (return to hospital)	n (%)	n (%)
Re-admissions to hospital (< 30 days)	n (%)	n (%)
Cause of reoperation		
Impaction of implant	n (%)	n (%)
Dislocation of implant	n (%)	n (%)
Foraminal re-stenosis	n (%)	n (%)
Wound infection	n (%)	n (%)
Wound opening	n (%)	n (%)
Other cause	n (%)	n (%)

Imbalance between the two groups in the crude incidence of safety concerns?

YES / NO

- If NO, our initial interpretation on efficacy (previous page) stands as is.
- If YES => We will add the following notion about the imbalance (excess in harms) to our interpretation:

"*However, there was a noteworthy imbalance in the incidence of safety concerns in the two treatment strategies (higher/lower rate in Group A) and this should be considered when interpreting the trial findings.*"

3. Unblinding

After consideration of the major downsides of the two treatment groups, we have now reached a consensus on our blinded assessment on efficacy.

Our statistician will now unblind the treatment group assignment (break the randomization code):

Group A = Inpatient care / Outpatient care [incorrect option to be removed]
Group B = Inpatient care / Outpatient care [incorrect option to be removed]

Given the above noted, the FACADE data is shown in **Table 1** (with n-values for Groups to be added) and in Scenario 1 (**Figure 2**) or Scenario 2 (**Figure 3**). [incorrect option to be removed]

Table 2. Primary outcome at the primary outcome assessment time point (6 months).

Table 2. Primary outcome at six months					
	Group A		**Group B**		**Difference (95% CI)**
		Mean ± SE		Mean ± SE	
Primary efficacy outcome					
Neck Disability Index (Scale: 0 to 100)		?? ± ??		?? ± ??	?? ± ??
***Means and standard errors are derived from a general linear repeated measures model analysis.** **Abbreviations: CI: Confidence Interval; SE: Standard Error**					

Figure 2 or **Figure 3**

4. Unblinded interpretation on efficacy and clinical relevance

Accordingly, our interpretation of the FACADE trial is as follows:

[incorrect options to be removed]

(1) Inpatient care is superior to outpatient care after anterior cervical decompression and fusion. However, be it noted that we did not set a superiority hypothesis in the study protocol.

OR

(2) Inpatient care is non-inferior to outpatient care after anterior cervical decompression and fusion.

OR

(3) Inpatient care is inferior to outpatient care after anterior cervical decompression and fusion.

OR

(4) Our results are inconclusive regarding the non-inferiority of the two groups after anterior cervical decompression and fusion.

In addition to the primary conclusion above, the following notion regarding downsides of the two treatments will / will not be added [incorrect option to be removed] based on our assessment of the need for safety concerns (Section 2):

“However, there was a noteworthy imbalance in the safety of the two treatment strategies (higher/lower [incorrect option to be removed] rate in Outpatient care) and this should be considered when interpreting the trial findings.”

5. Final interpretation
Our final interpretation of the FACADE trial stands as follows:

[Copy & paste the correct interpretation]

Place: ZOOM-/Teams-meeting
Time: [Insert date here]

_____
Teppo Järvinen

_____
Simo Taimela

_____
Tomasz Czuba, trial statistician

<u>Also present at the meeting (as external observers):</u>

_____
Kimmo Lönnrot, MD, PhD

_____
Rahul Raj, MD, PhD

_____
Jarno Satopää, MD, PhD