Super-FIN Trial

Plan for Blinded data interpretation

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18.7.2022

We, the Blinded Data Interpretation Committee of the SUPER-Fin trial, have reached a consensus on how to carry out the blinded data interpretation (BDI).

The document coined "Minutes for Super-Fin blinded data interpretation" (next page) outlines the execution of the blinded data interpretation for the SUPER-Fin trial.

Statistical analysis will be carried out by the trial statistician without any involvement from members of the Blinded Data Interpretation Committee or other Super-Fin 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 initial non-surgical treatment strategy and one where Group A is the initial surgical 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. Kortekangas and Lehtola 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 Super-Fin 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.

Super-Fin Blinded Data Interpretation Committee July 18, 2022

Teppo Järvinen, MD, PhD (Chair)

Simo Taimela, MD, PhD (Co-Chair)

Pasi Ohtonen, Trial statistician

Harri Pakarinen MD, PhD

Tero Kortekangas, MD, PhD

Ristomatti Lehtola, MD

Minutes for the Blinded Data Interpretation meeting for Manuscript:

Surgery versus Non-surgical Treatment for ER-stress Unstable Weber-B Unimalleolar Fractures (Super-Fin): A Prospective Randomised Non-Inferiority Trial

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Background and trial objectives

Super-Fin is a prospective randomised non-inferiority trial designed to compare two different treatment strategies: surgery (open reduction and plate fixation) vs. non-surgical treatment (cast immobilisation for 6 weeks) in patients with an ER-stress positive unimalleolar ankle fracture.

Our hypothesis is that non-surgical treatment yields non-inferior functional outcome to surgery, with no excess incidence of harms by potentially avoiding complications related to surgery. Non-inferiority of the non-surgical treatment with respect to surgery is of interest as non-surgical treatment has some other benefits,[1]such as being less burdensome to the patients and the healthcare system.

The primary, non-inferiority, intention-to-treat outcome is the Olerud-Molander Ankle Score (OMAS),[2] at 24 months.

We consider non-inferiority proven if ankle function in the initial non-surgical treatment strategy, as determined by OMAS, is within the pre-defined non-inferiority margin of the surgery group and there is no significantly increased risk of harms. Our predefined non-inferiority margin for the primary outcome at the primary assessment time point is set at 8 points.

Sample size

The sample size calculation was performed for a two-arm study (surgery vs non-operative treatment). In our previous study assessing surgery for unstable ankle fractures with the same primary outcome,[3] the mean OMAS score was 79.6 (SD 15.5) at the 2-year follow-up. During the design of the present trial, no estimate for minimal clinically relevant change existed for OMAS. In the absence of better evidence, we organized a focus group discussion among experts to define the appropriate estimate for non-inferiority margin. The panel reached a consensus that a 10% difference in 0–100 OMAS scale would not be clinically significant, which was then used to derive our non-inferiority margin (10% equals eight points in the OMAS scale, Cohen's $d=0.215$, indicating a small effect size). With $\alpha=0.05$, power 80% ($1-\beta=0.8$), a non-inferiority margin of 10% (8 points), and with a dropout rate of 20%, the calculations resulted in 63 patients per group (total n=126).

Statistical analysis

Primary analysis

The trial was primarily designed to ascertain whether initial non-surgical treatment is non-inferior to initial surgery, 2 years after the injury, with the primary outcome, the OMAS. Only the primary analysis, initial non-surgical treatment versus initial surgery, will be used to assess non-inferiority. For the primary time point, non-inferiority of non-surgical treatment to surgery will be claimed if the lower limit of the confidence interval (for differences in means in OMAS) is greater than −8.0 in the primary comparison. According to the CONSORT statement for non-

inferiority and equivalence,[1] secondary outcomes can be managed using either a superiority or an equivalence framework. In our trial, all secondary outcomes will be assessed with a superiority hypothesis, but as the trial was not powered for these comparisons, we will merely consider the data (analyses) as supportive, exploratory, and/or hypothesis generating.

The primary analysis will be performed according to the intention-to-treat principle. In the intention-to-treat analyses, the participants will be included as randomised. The results will be reported following the Consolidated Standards of Reporting Trials (CONSORT) statement. [1,4] We will quantify the treatment effect on an intention to treat basis as the absolute difference between the groups in the OMAS score (primary outcome) with the associated 95% confidence intervals and P values at 24 months after the randomisation (primary time point).

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, Super-Fin statistician (PO) will carry out the statistical analyses, blinded to the group assignment, and presents the data as Group A and Group B. The Super-Fin 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 Super-Fin 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 non-surgical treatment (cast immobilisation) non-inferior to surgery?

- Table 1. Baseline characteristics.
- Figure 1. Trial flowchart.
- Table 2. Primary outcome (OMAS) at the primary outcome assessment time point.

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

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

Although we maintain that ankle function is the most valid outcome for assessing the success of treatment of patients with an ankle fracture (as any deviations from optimal course of healing should ultimately be apparent in ankle function), we acknowledge the need to consider the inherent downsides of both treatment strategies before making our final interpretation.

The primary concern related to initial non-surgical treatment of unstable ankle fractures is an increased risk of ankle mortise becoming incongruent, which – if left untreated – predisposes the patients to early post-traumatic osteoarthritis and poor function.[6–13]

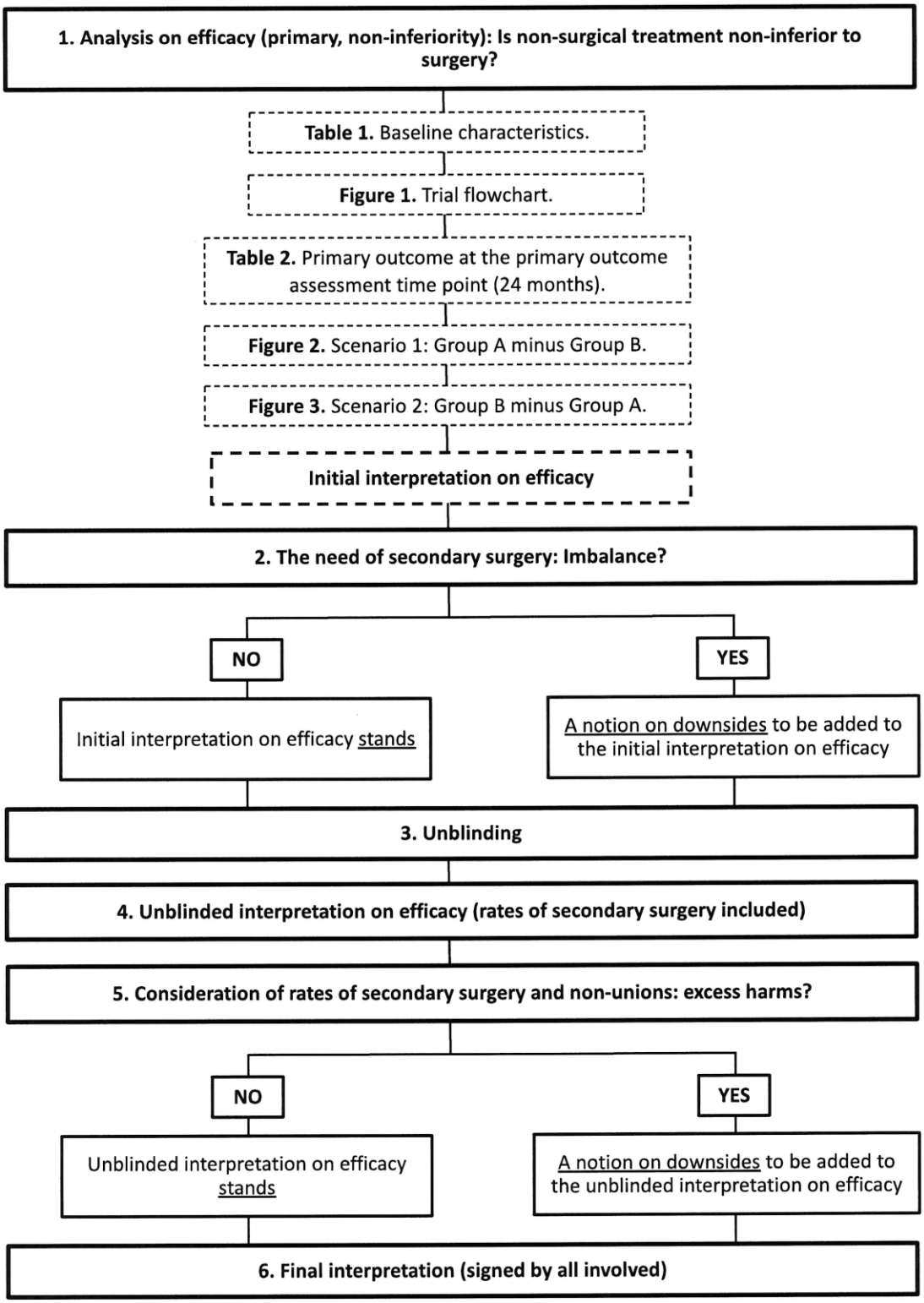
Surgery, in turn, is an invasive procedure per se, and is thus associated with both perioperative and postoperative risks. Based on existing literature, the overall incidence of adverse consequences related to ankle fracture surgery varies from 1% to 40 % depending on severity of the soft tissue injury, comorbidities, and age of the patients.[14–16] Of these, the risk of postoperative wound complications ranges from 6.1 to 10% in unselected patient materials.[15,17–19]

In the only previous study with a similar design to the SUPER-Fin trial,[20] 40% of 40 patients in the non-surgical group reported had "compromised fracture healing": namely, eight fracture displacements and eight with a delayed or non-union. However, only two of these patients required secondary surgery. In the surgery arm, in turn, six patients experienced a post-operative wound infection, but only one required a secondary surgery to revise the wound. In addition, there were four patients treated initially with surgery that required a secondary surgery to remove a symptomatic hardware.

Although data on the exact incidences and long-term effects of downsides/adverse consequences of both treatment strategies is scarce, it seems highly likely that our analysis will be underpowered. Furthermore, both treatment strategies have unique, characteristic adverse consequences that would likely unblind the treatment given for outcome assessors and/or those interpreting the data.

For the above noted reasons, particularly to preserve blinding, we have decided to only assess the incidence of secondary surgery in both groups in our primary efficacy analysis, as we consider this outcome to be most appropriate (blinding-preserving) for comparing the major downsides of the two treatment strategies. However, to be completely transparent and inclusive about the possible effect of adverse consequences on the clinical relevance (interpretation) of our findings, we commit to also considering the rate of non-unions before finalising our interpretation. However, this more comprehensive analysis on the downsides of the two treatments will not change our assessment **on efficacy**, rather possibly only change the wording of a possible notion on adverse consequences, and accordingly, it will be carried out after we have reached a consensus on efficacy (and unblinded the treatment assignment = broken the randomization code).

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

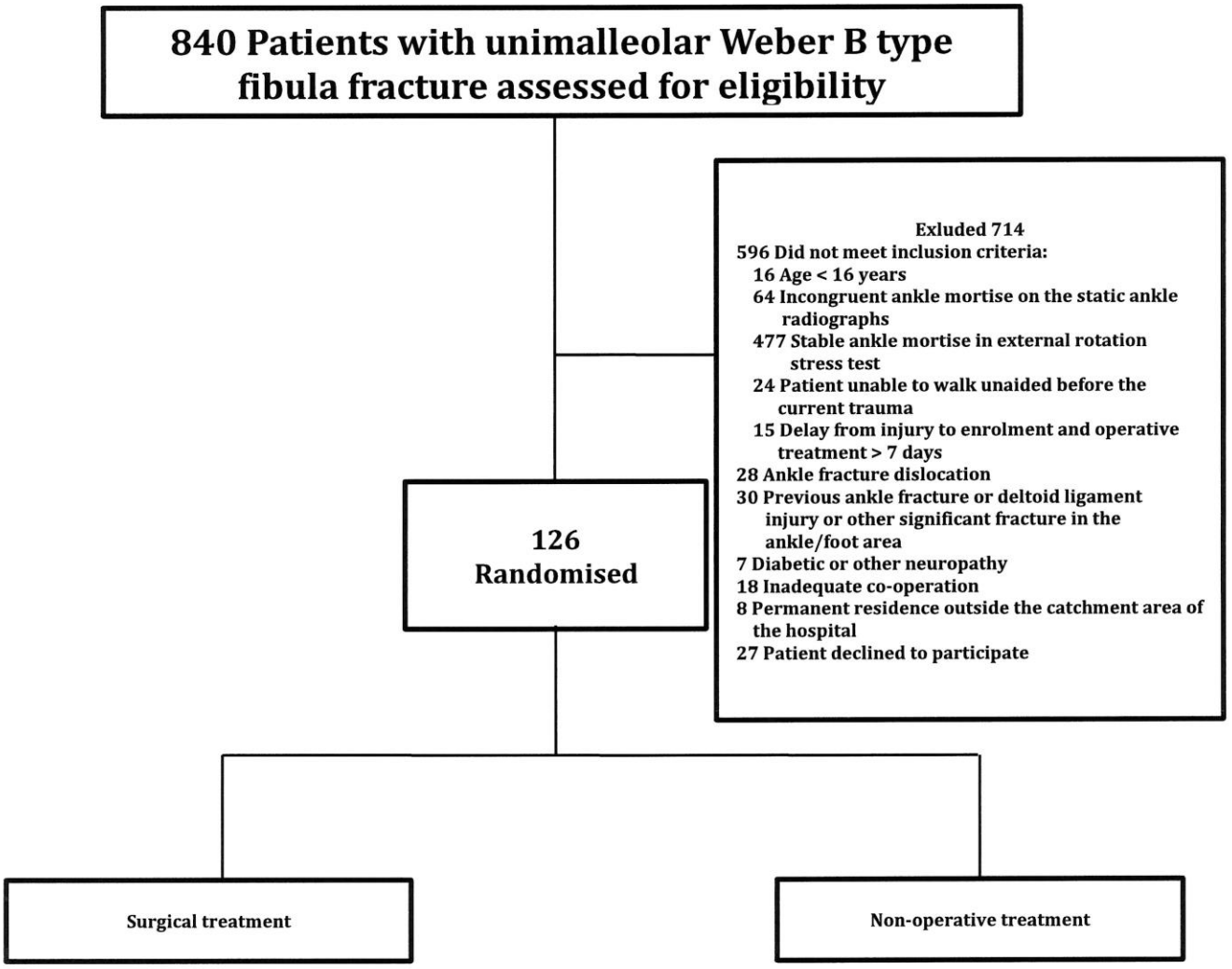

1. Analysis on efficacy (primary, non-inferiority): Is non-surgical treatment non-inferior to surgery?
Table 1. Baseline characteristics.
Figure 1. Trial flowchart.
Table 2. Primary outcome at the primary outcome assessment time point (24 months).
Figure 2. Scenario 1: Group A minus Group B.
Figure 3. Scenario 2: Group B minus Group A.
Initial interpretation on efficacy
2. The need of secondary surgery: Imbalance?
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 (rates of secondary surgery included)
5. Consideration of rates of secondary surgery and non-unions: excess harms?
NO
YES
Unblinded interpretation on efficacy stands
A notion on downsides to be added to the unblinded interpretation on efficacy
6. Final interpretation (signed by all involved)

1. Analysis on efficacy (primary, non-inferiority): Is non-surgical treatment non-inferior to surgery?

Table 1. Baseline characteristics.

Characteristic	**Group A (n = ??)**	**Group B (n = ??)**
Age at fracture years, mean (SD) [range]		
Patients aged over 50 years, No. (%)		
Gender, No. (%)		
Men		
Women		
Level of education*, No. (%)		
Basic education (ISCED 2)		
Upper secondary education (ISCED 3–4)		
Short-cycle tertiary education (ISCED 5)		
Bachelor, Master or Doctoral (ISCED 6–8)		
Did not wish to answer or missing		
Place of occurrence (ICD-10) †, No. (%)		
Leisure activity		
Working for income		
Sports activity		
Other		

Figure 1. Trial flowchart (participant numbers to the point of randomization – not beyond, to preserve blinding)



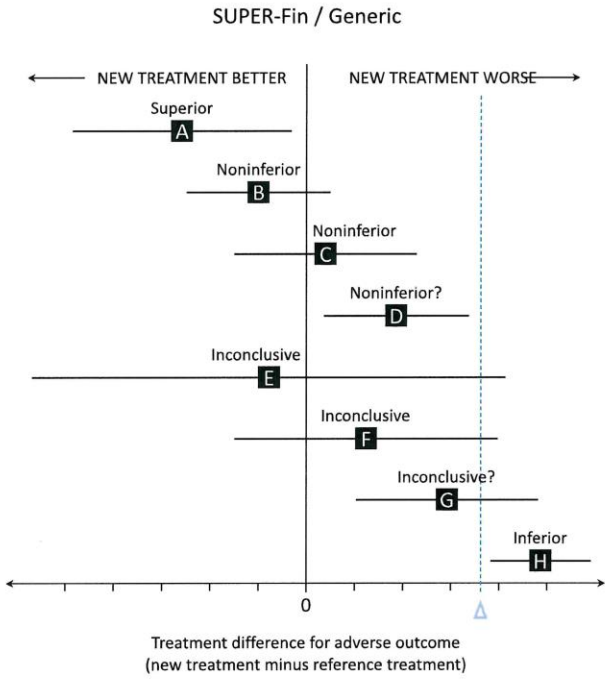
ITT, intention-to-treat; ER, external rotation; OMAS, Olerud-Molander Ankle Outcome Score.

Table 2. Primary outcome at the primary outcome assessment time point (24 months).[a]

Table 2. Primary outcome (OMAS) at 24 months					
	Group A		**Group B**		**Difference (95% CI)**
	n	Mean ± SD	n	Mean ± SD	
Primary efficacy outcome					
OMAS (Scale: 0 to 100)	TBA*	?? ± ??	TBA*	?? ± ??	?? ± ??
Abbreviations: CI: Confidence Interval; n: Number; SD: Standard Deviation					

* TBA (to be added, later): To preserve blinding, n-values for Groups A and B will only be added after randomization code is broken.

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[2].



As we will not have knowledge of treatment group assignment (whether Group A or Group B is our "new treatment": here, non-surgical treatment), 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 SUPER-Fin trial data).

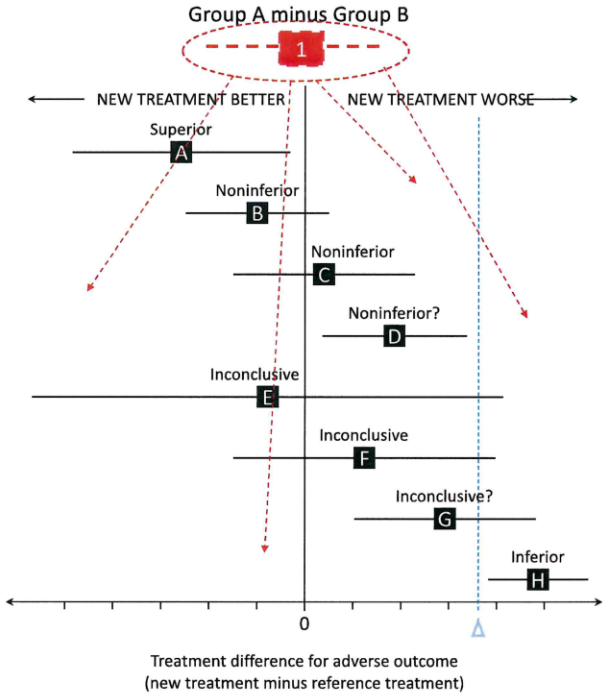
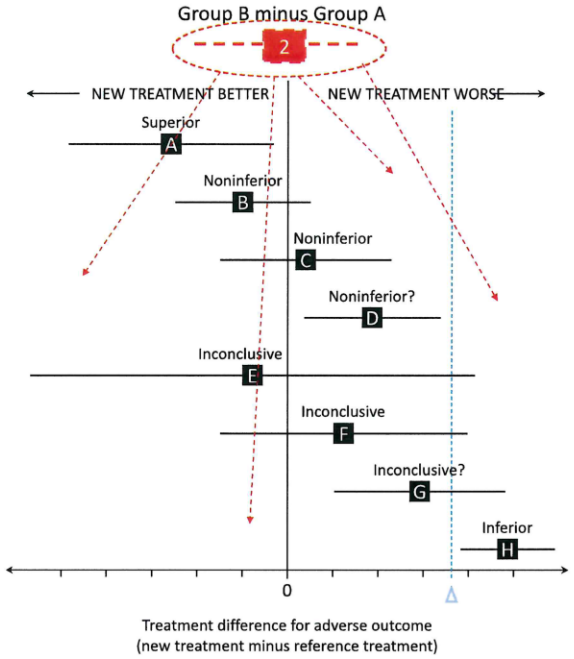


Figure 3. Scenario 2: Group B minus Group A.

(EXAMPLE GRAPH BELOW, to be replaced by the actual graph of the SUPER-Fin 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 non-surgical treatment (vs. surgery), is as follows:

Scenario 1 (Figure 2)

Group A is [superior A / non-inferior B to D / inferior H] to Group B in the treatment of ER-stress unstable Weber-B unimalleolar ankle fractures.

OR

Our results are inconclusive [E to G] regarding the non-inferiority of the two groups in the treatment of ER-stress unstable Weber-B unimalleolar ankle fractures.

Scenario 2 (Figure 3)

Group B is [superior A / non-inferior B to D / inferior H] to Group A in the treatment of ER-stress unstable Weber-B unimalleolar ankle fractures.

OR

Our results are inconclusive [E to G] regarding the non-inferiority of the two groups in the treatment of ER-stress unstable Weber-B unimalleolar ankle fractures.

2. Need for secondary surgery in the two treatment strategies?

	No.*		
	Group A	Group B	P-value
Secondary surgery	?	?	

* Given that the treatment groups should be quite balanced, we refrain from laying out the percentages and simply rely on crude n-values at this stage.

Imbalance between the two groups in the need for secondary surgery? 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 need for secondary surgery between 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 = Non-surgical treatment / Surgery [incorrect option to be removed]
Group B = Non-surgical treatment / Surgery [incorrect option to be removed]

Given the above noted, the SUPER-Fin 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 (24 months).

Table 2. Primary outcome (OMAS) at 24 months					
	Group A		**Group B**		**Difference (95% CI)**
	n	Mean ± SD	n	Mean ± SD	
Primary efficacy outcome					
OMAS (Scale: 0 to 100)	TBA	?? ± ??	TBA	?? ± ??	?? ± ??
Abbreviations: CI: Confidence Interval; n: Number; SD: Standard Deviation					

4. Unblinded interpretation on efficacy after consideration of the need for secondary surgery in the two treatment strategies

Accordingly, our penultimate interpretation of the SUPER-Fin trial is as follows:

[incorrect options to be removed]

(1) Non-surgical treatment is superior to surgery in the treatment of ER-stress unstable Weber-B unimalleolar ankle fractures. However, be it noted that we did not set a superiority hypothesis in the study protocol.

OR

(2) Non-surgical treatment is non-inferior to surgery in the treatment of ER-stress unstable Weber-B unimalleolar ankle fractures.

OR

(3) Non-surgical treatment is inferior to surgery in the treatment of ER-stress unstable Weber-B unimalleolar ankle fractures.

OR

(4) Our results are inconclusive regarding the non-inferiority of the two groups in the treatment of ER-stress unstable Weber-B unimalleolar ankle fractures.

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 secondary surgery (Section 2):

"*However, there was a noteworthy imbalance in the need for secondary surgery between the two treatment strategies (higher/lower rate in Group A) and this should be considered when interpreting the trial findings.*"

To finalise our interpretation, we will proceed into unblinded assessment of all downsides related to both treatments (Section 5., next page).

5. Consideration of <u>non-unions</u> (in addition to secondary surgery) of the two treatment strategies

	No. (%)		
	Group A	Group B	P-value
Non-union at 24 months Asymptomatic Symptomatic	 ? (?%) ? (?%)	 ? (?%) ? (?%)	 .???
Secondary surgery	?	?	

We note that the rate of non-unions – if dramatically different – could theoretically tilt the previously observed (im)balance in the incidence/risk of downsides of the two treatment groups. For the sake of transparency, we commit to considering the rate of non-unions but maintain that if not symptomatic enough to require secondary surgery, their clinical relevance is limited and will only require possible slight modification to our cautionary tail.

Imbalance between the two groups in all treatment-related downsides? YES / NO

- If NO, our final 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 harms between the two treatment strategies favoring non-surgical treatment / surgery* [incorrect option to be removed] *and this should be considered when interpreting the trial findings.*"

6. Final interpretation

After consideration of all harms, our final interpretation of the SUPER-Fin trial stands as follows:

[Copy & paste the correct interpretation]

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

Tero Kortekangas | Ristomatti Lehtola | Simo Taimela

Teppo Järvinen | Harri Pakarinen

Pasi Ohtonen, trial statistician

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