TEMPLATE RESEARCH PROTOCOL

(September 2018)

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics
- Sept 2018: adaptation section 12.1 and comment [CCMO46] due to applicability GDPR as of May, 2018

PROTOCOL TITLE 'Perioperative Lipofilling in Operative Treatment of Proximal Phalanx Fractures and Related Tenolysis: Improving Range of Motion'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AR	Adverse Reaction
AROM	Active Range of Motion
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CRIF	Closed Reduction and Internal Fixation
CV	Curriculum Vitae
DASH	Disabilities of the Arm, Shoulder and Hand
DIP-joint	Distal interphalangeal joint
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MCP-joint	Metacarpophalangeal joint
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische

	toetsingscommissie (METC)
NRS	Numeric (Pain) Rating Scale
ORIF	Open Reposition and Internal Fixation
PROM	Passive Range of Motion
PIF	Patient Information Form
PIP-joint	Proximal interphalangeal joint
ROM	Range of Motion
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAM	Total Active Motion
TMF	Trial Master File
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Hand fractures are a common clinical problem worldwide (1, 2) and account for a substantial economic burden and workload for experienced hand surgeons (3, 4). With regard to metacarpal and phalangeal fractures, surgery might be indicated in case of dislocation and/or instability to restore functionality through closed or open reduction and adequate stabilization by fixation (5-14). Unfortunately, tendon adhesions after operative treatment of these hand fractures remain a common complication (15-24); especially after open reposition and internal fixation (ORIF) of proximal phalanx (P1) fractures. This results in postoperative stiffness and thus decreased digital function. In case of insufficient digital function, tenolysis of the flexor and/or extensor tendons could be considered once the fracture is consolidated and competent hand therapy for at least 3 months seems ineffective (31). Several studies have focused on perioperative measures to prevent tendon adhesions and related stiffness after operative treatment of hand fractures avoiding tenolysis (32-37). These prophylactic measures include for example adhesion barriers, anti-adhesion membranes and adipofascial flaps, which could possibly improve the postoperative range of motion if further research is conducted. Only one of these studies, using an adipofascial flap as a tendon-gliding system after ORIF of P1 fractures, found a significant difference regarding postoperative range of motion (37). Related to the use of adipose tissue, lipofilling has been proven to be a promising technique in the treatment of scars/adhesions, especially in burn wounds (40-42). Recent studies even demonstrated the role of fat grafting in hand surgery, including scar management and tenolysis (43-47). Despite these promising results, no previous research has evaluated the use of perioperative lipofilling during surgical treatment of hand fractures or related tenolysis. Therefore, it might be that lipofilling could result in an improvement of postoperative motion and prevent and/or improve tenolysis due to providing a gliding surface for tendons.

Objective:

The aim of the two separate studies is as follows:

1. To evaluate the effect of perioperative lipofilling in patients with ORIF of P1 fractures on postoperative range of motion

2. To evaluate the effect of perioperative lipofilling in patients with tenolysis after operative treatment of P1 fractures on postoperative range of motion

Study design: a double-blinded randomized controlled trial

Study population:

1. Patients (age 18-65) with a single radiologically proven P1 fracture with an indication for ORIF

2. Patients (age 18-65) with limited digital function after operative treatment of a P1 fracture

with an indication for tenolysis

Intervention: patients will either receive 1ml of subcutaneous lipofilling or 1ml subcutaneous 0,9% NaCl around the operation site at the end of the ORIF or tenolysis

Main study parameters/endpoints:

1. In case of an indication for ORIF of P1 fractures the following parameters will be assessed:

- Preoperative
    - Total active motion (TAM) of the contralateral unaffected digit;
    - Active range of motion (AROM) and passive range of motion (PROM) of the metacarpophalangeal, proximal interphalangeal and distal interphalangeal (MCP-, PIP- and DIP) joint of the contralateral unaffected digit.
- 2 weeks, 6 weeks, 3 months and 6 months postoperative
    - NRS-score of the abdominal donor site.
- 6 weeks, 3 months and 6 months postoperative
    - TAM of the operated digit and the contralateral unaffected digit;
    - AROM and PROM of the MCP-, PIP- and DIP-joint of the operated digit and the contralateral unaffected digit;
    - MHQ-score.
- 6 months postoperative
    - Radiographic union outcomes of the operated digit.
- During the 6 months postoperative period
    - Postoperative complications, including infection, wound-related problems and stiffness;
    - Number of secondary procedures, including revision surgery and tenolysis.

2. In case of tenolysis after operative treatment of P1 fractures the following parameters will be assessed:

- Preoperative
    - TAM of the affected digit and the contralateral unaffected digit;
    - AROM and PROM of the MCP-, PIP- and DIP-joint of the affected digit and the contralateral unaffected digit;
    - MHQ-score.
- 2 weeks, 6 weeks, 3 months and 6 months postoperative
    - NRS-score of the abdominal donor site.
- 6 weeks, 3 months and 6 months postoperative
    - TAM of the operated digit and the contralateral unaffected digit;
    - AROM and PROM of the MCP-, PIP- and DIP-joint of the operated digit and the contralateral unaffected digit;

    - MHQ-score.
- During the 6 months postoperative period
    - Postoperative complications, including infection, wound-related problems and stiffness.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

1. Preoperatively, no additional procedures are added to the usual care.

In case of perioperative lipofilling, a minimal amount of autologous fat will be manually harvested perioperatively from the subdermal fat layer of the lower abdomen using very fine harvesting cannulas under additional tumescent anesthesia. The harvested autologous fat will be processed for injection by centrifugation and emulsification. The harvested and micronized autologous fat will be injected subcutaneous at the operation site after wound closure.

With regard to the control group, autologous fat of the lower abdomen will be harvested, but only 0,9% NaCl will be injected subcutaneous at the operation site after wound closure.

In addition to the regular postoperative follow-up including competent hand therapy, patients will complete the MHQ and rate their pain using a NRS-score (0-10 scale) of the abdominal donor site.

2. Preoperatively, patients will complete the MHQ (48, 49) in addition to the usual care. The duration of this questionnaire is estimated at 15-30 minutes.

In case of perioperative lipofilling, a minimal amount of autologous fat will be manually harvested perioperatively from the subdermal fat layer of the lower abdomen using very fine harvesting cannulas under additional tumescent anesthesia. The harvested autologous fat will be processed for injection by centrifugation and emulsification. The harvested and micronized autologous fat will be injected subcutaneous at the operation site after wound closure.

With regard to the control group, autologous fat of the lower abdomen will be harvested, but only 0,9% NaCl will be injected subcutaneous at the operation site after wound closure.

In addition to the regular postoperative follow-up including competent hand therapy, patients will complete the MHQ and rate their pain using a NRS-score (0-10 scale) of the abdominal donor site.

Lipofilling is generally considered safe; however, like any surgical intervention, minor complications can occur with a low rate (38-40). Fortunately, the complication rate with lipofilling is extremely low when compared to most open surgical methods. Moreover, the likelihood of complications decreases significantly with the surgeon’s experience.

1. INTRODUCTION AND RATIONALE

Hand fractures are common and metacarpal and phalangeal fractures account for more than 40% of all upper extremity fractures (1, 2). These fractures result in a substantial medical workload and socioeconomic burden (3, 4). The principle of treatment of these fractures is to restore functionality through anatomic reduction, adequate stabilization and minimizing additional soft tissue damage. If these aspects cannot be achieved by closed reduction and immobilization, operative treatment might be considered to optimize functional outcomes after shared decision making (2, 5, 6).

Surgical management of metacarpal and phalangeal fractures could involve closed reduction and internal fixation (CRIF) by percutaneous pinning (7-9) with minimal soft tissue damage and low infection risk. However, early mobilization is hindered because percutaneous pinning is often not stable for early practice. Open reduction and internal fixation (ORIF) by plate and/or (intramedullary) screws (10, 11) is often indicated in comminuted or intra-articular fractures, irreducible fractures, fractures with segmental bone loss and open fractures. Unfortunately, ORIF leads to more soft tissue damage. On the other hand, early mobilization is possible (5, 12). If these treatment options are not sufficient dynamic or static external fixation (13, 14) could be indicated.

Operative treatment of hand fractures can be challenging due to the complex anatomy of the hand comprising bones, joints and surrounding soft tissues. Unfortunately, postoperative complications are not uncommon and complication rates are reported up to 64% (15). The most relevant and commonly reported complication is stiffness and thus decreased digital function, other complications are malunion, posttraumatic arthritis, nonunion, infection and chronic pain (15-24). Stiffness with solely active motion indicates adhesions to surrounding soft tissues, osseous and articular structures or osteosynthesis, whereas both limited active and passive motion suggest additional capsuloligamentous contractures (25). Predisposing factors include trauma-related factors such as open fractures, crush injuries with surrounding soft tissue injuries and multiple finger injuries (15, 20, 21, 26-28). In addition, treatment-related factors such as increased soft tissue damage during fracture surgery results in increased risk of postoperative stiffness.

Postoperative stiffness could be prevented or treated through intensive hand therapy by a skilled hand therapist and a co-operative patient to gain as much postoperative motion as possible (29, 30). In case of insufficient motion, tenolysis of the flexor and/or extensor tendons

could be considered, but not before consolidation of the fracture is achieved and competent hand therapy for at least 3 months is given (31). A recent systematic review by de Vries et al. (*to be published*) showed an incidence ranging from 4-32% of tenolysis after operative treatment of proximal phalanx (P1) fractures; mainly focusing on open reduction and internal fixation.

However, several animal and clinical studies have focused on perioperative procedures to prevent tendon adhesions and related stiffness after operative treatment of hand fractures and hence prevent tenolysis. These studies focused on different perioperative prophylactic methods to allow properly gliding of the tendons postoperatively, including adhesion barriers, anti-adhesion membranes and adipofascial flaps. Kappos et al. (32) analysed the effect of a denaturated cellulose adhesion barrier after plate osteosynthesis of P1 fractures in a randomized clinical setting on total active motion (TAM), Disabilities of the Arm, Shoulder and Hand (DASH)-scores and secondary operations such as tenolysis. The use of an adhesion barrier did not significantly improve postoperative TAM in comparison to the absence of an adhesion barrier; even the adhesion barrier did not lead to fewer secondary procedures. Von Kieseritzky et al. (33, 34) studied the use of an adhesion barrier in both rabbits (DendoPrime) and patients (Dynavisc) in plate fixation of phalangeal fractures. Although the study in rabbits (33) concluded that the barrier could improve range of motion and possibly reduce adhesions, the patient study (34) showed unconvincing results with regard to postoperative TAM. In the study of Sato et al. (35) the use of an anti-adhesion membrane was studied in a rabbit model, which macroscopically resulted in a significantly lower adhesion in the membrane group than in the control group. Lucchina et al. (36, 37) focused on using an adipofascial flap to prevent adhesions after plating of P1 fractures. A patient study (37) showed a mean postoperative TAM of 205° (SD: 38°) using an adipofascial flap in comparison to a mean postoperative TAM of 156° (SD: 45°) in the control group. Using a Bayesian approach, a probability of 99% (Bayes Factor: 91.11) was given in favor of a positive effect of the use of an adipofascial flap to improve postoperative TAM.

Additionally, the concept of using adipose tissue to treat tissue damage or consequences of tissue damage has been studied before, especially in the aspect of grafting (autologous) adipose tissue; called lipofilling. This promising technique has been developed in the recent years and is supported by in vitro studies, animal studies and evidence-based clinical trials. In first instance, previous research focused on correcting subcutaneous volume deficits and related efficacy and safety, while recent research demonstrated an additional modulating role regarding scar tissue and tissue regeneration at the recipient site (38, 39). Therefore, lipofilling is used for multiple treatment options nowadays, including scars/adhesions due to burn

wounds, trauma, previous surgery, and irradiation (40-42). Deptula et al. (43, 44) and Khouri et al (45) recently reported the application of autologous fat grafting in hand surgery such as burn/scar management and tenolysis. Cortes et al. (46) even demonstrated the efficacy of a minimally invasive tenolysis with lipofilling, resulting in improved postoperative TAM and improved pain scores in patients with stiff digits. In addition, Krześniak et al. (47) suggest that the usage of autologous fat grafting during secondary carpal tunnel release inhibits the scarring process in the carpal tunnel. Although previous studies have analysed the role of lipofilling in hand surgery, no previous research focused on grafting (autologous) adipose tissue in relation to operative treatment of hand fractures and related tenolysis.

Till this date, no clinical trial has been performed using perioperative lipofilling during surgical treatment of hand fractures or related tenolysis to prevent postoperative tendon adhesions by allowing adequate gliding of the tendons; possibly resulting in an improvement of postoperative motion. Therefore, the aim of the following two separate studies is:
1. To evaluate the effect of perioperative lipofilling in patients with ORIF of P1 fractures on postoperative TAM, active and passive range of motion (AROM/PROM), Michigan Hand Outcomes Questionnaire (MHQ)-scores, Numeric (Pain) Rating Scale (NRS)-scores of the abdomen and radiographic union outcomes.
2. To evaluate the effect of perioperative lipofilling in patients with tenolysis after operative treatment of P1 fractures on postoperative TAM, active and passive range of motion (AROM/PROM), Michigan Hand Outcomes Questionnaire (MHQ)-scores and Numeric (Pain) Rating Scale (NRS)-scores of the abdomen.

2. OBJECTIVES

Primary Objective:
1. To evaluate the effect of perioperative lipofilling in patients with ORIF of P1 fractures on postoperative TAM of the operated digit.
2. To evaluate the effect of perioperative lipofilling in patients with tenolysis after operative treatment of P1 fractures on postoperative TAM of the operated digit.
Patients will be physically examined by the hand therapist or clinician 6 weeks, 3 months and 6 months postoperatively to assess the TAM of the operated digit.

Secondary Objective:
1. To evaluate the effect of perioperative lipofilling in patients with ORIF of P1 fractures on:
- Postoperative AROM and PROM of the metacarpophalangeal, proximal interphalangeal and distal interphalangeal (MCP-, PIP- and DIP-) joint of the operated

digit. Patients will be physically examined by the hand therapist or clinician 6 weeks, 3 months and 6 months postoperatively to assess the AROM and PROM of MCP-, PIP- and DIP-joint of the operated digit.

- Postoperative NRS-scores of the abdomen. Patients will rate the postoperative pain using NRS (0-10 scale) for the abdominal donor site 2 weeks, 6 weeks, 3 months and 6 months postoperative. NRS (0-10 scale) is used.
- Postoperative MHQ-scores. Patients will complete the MHQ (48, 49) 6 weeks, 3 months and 6 months postoperative.
- Postoperative radiographic union outcomes of the operated digit. Patients will undergo radiographic evaluation at 6 months postoperatively, during which the degree of union (non-union, malunion, or union) will be assessed.
- Postoperative complications, including infection, wound-related problems and stiffness during the 6 months postoperative period.
- The number of secondary procedures, including revision surgery and tenolysis, during the 6 months postoperative period.

2. To evaluate the effect of perioperative lipofilling in patients with tenolysis after operative treatment of P1 fractures on:

- Postoperative AROM and PROM of the metacarpophalangeal, proximal interphalangeal and distal interphalangeal (MCP-, PIP- and DIP-) joint of the operated digit. Patients will be physically examined by the hand therapist or clinician 6 weeks, 3 months and 6 months postoperatively to assess the AROM and PROM of MCP-, PIP- and DIP-joint of the operated digit.
- Postoperative NRS-scores of the abdomen. Patients will rate the postoperative pain using NRS (0-10 scale) for the abdominal donor site 2 weeks, 6 weeks, 3 months and 6 months postoperative. NRS (0-10 scale) is used.
- Postoperative MHQ-scores. Patients will complete the MHQ (48, 49) 6 weeks, 3 months and 6 months postoperative.
- Postoperative complications, including infection, wound-related problems and stiffness, during the 6 months postoperative period.

3. STUDY DESIGN

Patient intake is done at the Department of Plastic Surgery of the Jeroen Bosch Hospital ‘s Hertogenbosch.

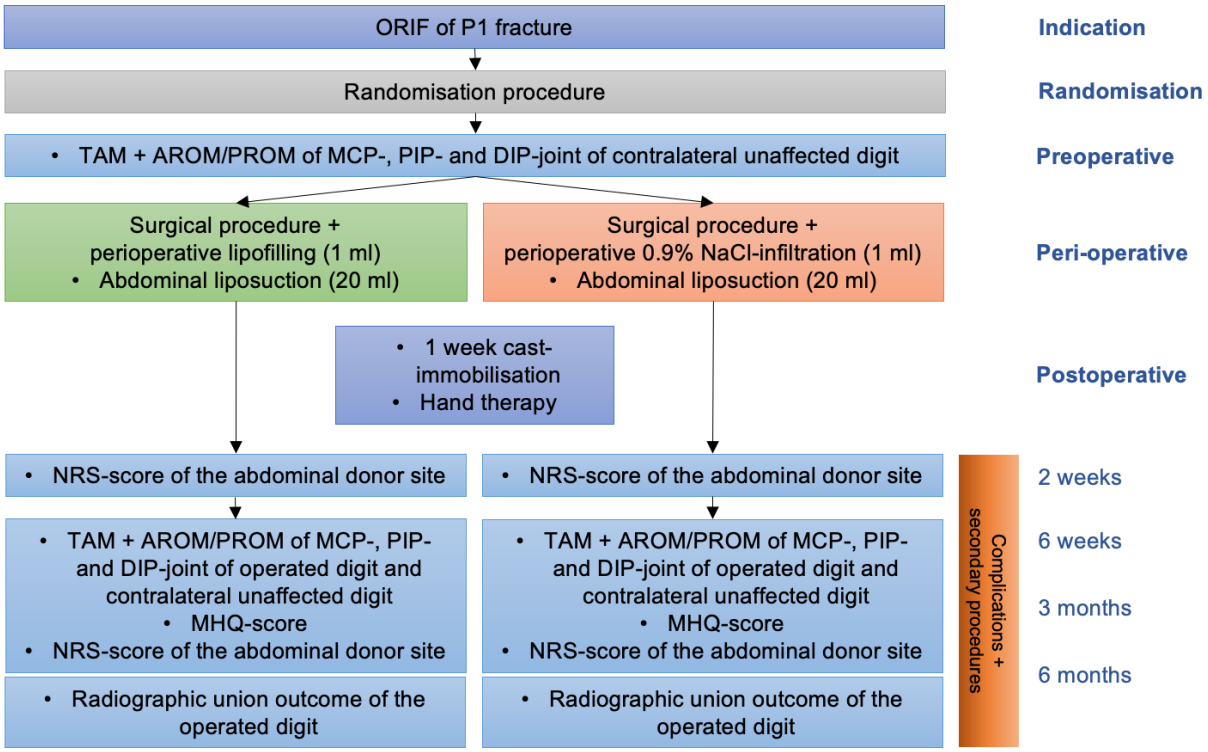


Figure 1A: study design double-blinded randomized controlled trial (ORIF)

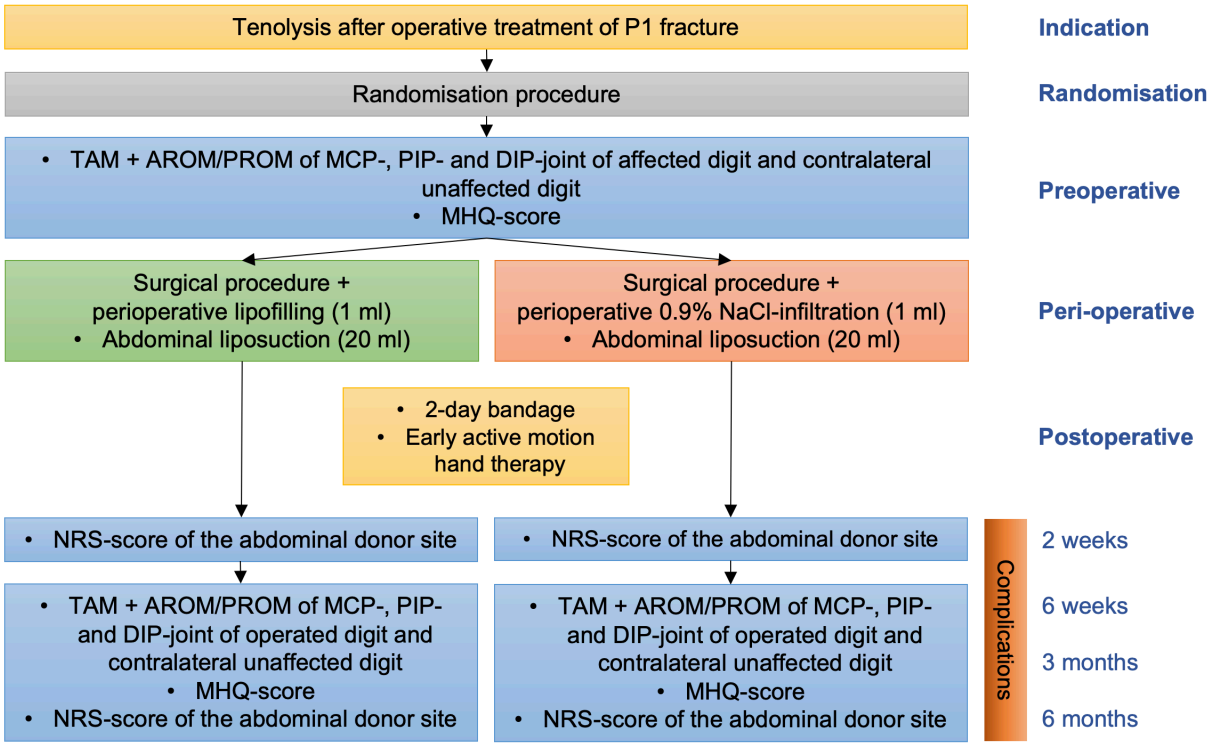


Figure 1B: study design double-blinded randomized controlled trial (tenolysis)

4. STUDY POPULATION

4.1 Population (base)

The population in these studies will consist of both male and female patients, aged 18-65, with:

1. A single radiologically proven P1 fracture with an indication for ORIF;
2. Limited digital function after operative treatment of a P1 fracture with an indication for tenolysis.

The inclusion of patients will be done at the outpatient clinic of the Department of Plastic Surgery at the Jeroen Bosch Hospital (‘s Hertogenbosch).

The clinicians, including the plastic surgeons or residents (not in training), will verify the eligibility criteria and inform the patient about the study. If a patient meets the inclusion criteria, he or she will be provided with the Patient Information Form (PIF) and the Informed Consent Form (ICF) for the study. These documents contain all information with respect to the study and the patient will be requested to read all information and discuss it with his or her family/GP. In case of an indication for ORIF, after 2 days the subject will be contacted about his/her decision regarding study participation (see “Chapter 11.2 Recruitment and consent” regarding the consideration period); for tenolysis, the patients will be contacted after 14 days of consideration. If a patient in free will decides to participate, he/she will sign the ICF with presence of one of the clinicians, receive a copy and the ICF will be put in the electronic medical chart.

4.2 Inclusion criteria

1. In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Aged 18-65 years
- Indication for ORIF due to a single radiologically proven P1 fracture
- Able to read and speak Dutch
- Mentally competent

2. In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Aged 18-65 years
- Indication for tenolysis due to limited digital function after former operative treatment of a P1 fracture
- Able to read and speak Dutch
- Mentally competent

4.3 Exclusion criteria

1. A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Concomitant tendinous or neurovascular injuries
- Prior pathology or surgical interventions of the affected digit in the previous year
- Prior pathology or surgical interventions of the contralateral digit
- A known psychiatric condition
- A known systemic disease and/or comorbidity that will impair wound healing (e.g. diabetes mellitus, known atherosclerosis with an event that required hospitalization, collagen diseases, diseases of the skin, HIV).
- Prednisone or another immunotherapy
- Smoking
- Pregnancy or active child wish

2. A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Concomitant tendinous or neurovascular injuries
- Prior pathology or surgical interventions of the affected digit in the previous year other than operative fracture fixation
- Prior pathology or surgical interventions of the contralateral digit
- Less than 3 months of competent hand therapy
- A known psychiatric condition
- A known systemic disease and/or comorbidity that will impair wound healing (e.g. diabetes mellitus, known atherosclerosis with an event that required hospitalization, collagen diseases, diseases of the skin, HIV).
- Prednisone or another immunotherapy
- Smoking
- Pregnancy or active child wish

4.4 Sample size calculation

The sample size calculation is based on the difference in scores of the primary measure of effect: the TAM of the operated digit between the lipofilling and control group at 6 months postoperative. TAM is described by the American Society for Surgery of the Hand (ASSH) as the sum of active MCP, PIP and DIP arc of motion in degrees of an individual digit (50, 51), of

which the norm is 260 degrees.

1. ORIF of proximal phalanx fractures

With regard to ORIF of proximal phalanx fractures, Lucchina et al. (37) showed, in a comparative study with a mean follow-up of 5.3 years, a significant difference in postoperative mean TAM-values between the control and the group using an adipofascial flap; respectively a mean TAM of 156 degrees (SD: 45°; median: 148°; IQR: 131°-174°) and 205 degrees (SD: 38°; median: 218°; IQR: 177°-232°). Unfortunately, no preoperative TAM-values were given.
Focusing on clinical relevance, we would expect a mean TAM difference of 35 degrees rather than ca. 50 degrees between the control and lipofilling group 6 months postoperative. Previous studies by Hume et al. and Bain et al. defined a functional TAM respectively as 165 degrees and 170 degrees (52, 53). Assuming a mean TAM of 165 degrees (52) 6 months after ORIF of P1 fractures without lipofilling, a mean TAM of 200 degrees 6 months postoperatively is expected for the lipofilling group.
Thus, based on a difference of 35 degrees, an SD of 40 degrees, assuming an alpha of 0.05, a power of 0.8 and a two-sided test. This results in a required sample of 22 patients per group, a total of 44 patients. Assuming a loss of 20% in follow-up, a sample of 56 patients is required (28 per group).

2. Tenolysis after operative treatment of proximal phalanx fractures

Based on the literature focusing on tenolysis after operative treatment of hand fractures, the mean preoperative TAM value of the affected digit is 160 degrees (54-56). Combining these studies, the mean increase in TAM of the operated digit is 65 degrees comparing pre- to post-tenolysis. However, the study of Misirlioglu et al. (55) is a case report, thus we expect a lower increase of 48 degrees based on the retrospective cohort study of Brei-Thoma et al. and Wong et al. (54, 56). Lutsky et al. (57) showed a mean increase in TAM of 41 degrees after operative intervention for finger stiffness caused by a fracture. However, in this study two of the 18 patients were treated by splinting/casting. To come to a representative score for the postoperative TAM value of the control group, we combined these outcomes (54, 56, 57) resulting in postoperative TAM value of 205 degrees after tenolysis. Unfortunately, no previous study defined the improvement of tenolysis including lipografting in terms of TAM values. Cortes et al. (46) only mentioned that the mean preoperative TAM was less than 75% before surgery and achieved 75% or greater postoperative. This results in a mean postoperative TAM value of 195 degrees or greater if a maximum postoperative TAM of 260 degrees is assumed. Focusing on clinical relevance, we would expect a mean TAM difference of 30 degrees between the control and lipofilling group 6 months postoperative. Assuming a mean TAM of

205 degrees 6 months after tenolysis without lipofilling, a mean TAM of 235 degrees 6 months postoperatively is expected for the lipofilling group. The reason for a lower mean TAM difference 6 months postoperative, in comparison to the ORIF-group (see above; 35 degrees), is based on a higher mean postoperative TAM of the control group (205 degrees) (56) and the aspect of a secondary surgical procedure.
Thus, based on a difference of 30 degrees, an SD of 40 degrees, assuming an alpha of 0.05, a power of 0.8 and a two-sided test. This results in a required sample of 29 patients per group, a total of 56 patients. Assuming a loss of 20% in follow-up, a sample of 74 patients is required (37 per group).

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Perioperatively, 20ml of lipoaspirate will be manually harvested, under additional tumescent anesthesia (i.e. a very diluted solution of lidocaine, adrenaline and sodium bicarbonate) (58) of an area with a diameter of ca. 15cm, from the subdermal fat layer of the lower abdomen using Arthrex ACP double syringes (Arthrex®, ACP System, Naples, FL, USA) and disposable instruments of the Arthrex ACA-kit. After harvesting, the lipoaspirate will be centrifuged (Hettich centrifuge (1206-ART)) at a G-force of 960G, emulsified by using a connector piece between two luerlock syringes and centrifuged again, after being transferred back in to the Arthrex ACP double syringe, to process the micronized autologous fat for injection (59). In case of lipofilling, 1ml of the harvested and micronized autologous fat will be injected subcutaneous at the operation site after wound closure. The amount of micronized autologous fat is based on the expected available subcutaneous space after closing the wound. With regard to the control group, only 1ml of 0,9% NaCl will be injected subcutaneous at the operation site after wound closure. For more information about NaCl solution see D2 SPC Natriumchloride. NaCl is a regular medicine under the responsibility of the hospital where the patient is treated. This procedure will take an additional 10 minutes of operation time.

5.2 Use of co-intervention (if applicable)

Not applicable.

5.3 Escape medication (if applicable)

Not applicable.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Lipofilling of grafted (autologous) adipose tissue.

6.2 Summary of findings from non-clinical studies

Lipofilling in animal studies

Experimental animal models for scarring have given insight in the influence of lipofilling to treat (dermal) scars. Scar aspect has been investigated in two studies using irradiation skin damage models in rodents (60, 61). Skin fibrosis after radiation treatment is a clinically relevant problem, which can easily be simulated in rodents. After radiation, dermatitis can develop, which eventually gives rise to fibrotic skin, which is characterized by epidermal thickening and irregular deposition of collagen in the dermis. Also, compared to normal skin, irradiated skin areas have an increased vessel density. In two studies in mice, it has been shown that treatment with lipografts can reduce all these hallmark features of irradiation-damaged skin (60, 61). In several studies focusing on burn wounds in mice (62-64), it has been shown that lipografting reduces skin fibrosis or scarring after burn injury and leads to better scar aspect; by increasing pro-angiogenic factors VEGF and SDF-1 and decreasing pro-fibrotic factor TGF-β118 (62). Thus, it can be concluded that lipofilling in rodent models for (skin) fibrosis, lipografting reduces adverse fibrotic changes in the tissue. This appears to be mediated by factors in the lipograft that can inhibit activation of fibrotic and inflammatory signal transduction pathways.

6.3 Summary of findings from clinical studies

Lipofilling in clinical studies

In 3 recent systematic reviews (and meta-analysis) focusing on clinical studies (41, 42, 65), autologous fat grafting to treat fibrosis and scar-related conditions has been shown effective. The use of lipofilling results in a significant improvement of scar aspect and skin characteristics; a.o. based on the evaluation using the Patient and Observer Scar Assessment Scale. In two of the reviews (41, 42), lipofilling even resulted in a significant pain reduction based on the Visual Analog Scale.

Negenborn et al. (41) mentioned only limited side effects, such as superficial abdominal haematoma, postlipofilling edema lasting up to maximally 1 month, infection (successfully treated with antibiotics), temporary hyperpigmentation (disappeared within 3 months) and re-injection of autologous fat. In the review of Krastev et al. (42), minor complications occurred in 4.8% of the procedures, including donor-site contour deformity, palpable mass, infection, haematoma and seroma.

In conclusion, autologous fat transfer for treatment of scar-related conditions provides beneficial effects with a low rate of clinical complications. However, for the future all aforementioned reviews recommend high-level evidence studies such as, randomized controlled trials (RCTs) and cohort studies; for evaluating long-term effects.

Lipofilling in hand-related clinical studies

Moreover, previous research has shown that lipofilling is a promising treatment for several conditions with regard to hand surgery.

Krześniak et al. (47) proposed the use of autologous fat grafting during secondary carpal tunnel release to inhibit the scarring process. Fat was harvested from the lower abdomen and grafted into the scarred transverse carpal ligament and surrounding tissue. The examination demonstrated that the sensory severity score and the functional severity score decreased significantly between the preoperative values and those observed at 12-month postoperative follow-up. No complications occurred in this study.

Other review articles (43-45) show that lipofilling for (burn) scar contracture in the hand results in improved scar quality and reduced adhesions to underlying tendons. As a result, patients could gain range of motion. Deptula et al. (43) showed a low rate of complications ranging from 0 to 7.6% with minor complications such as edema, haematoma, paresthesia and infection responsive to oral antibiotics. In 2022, Deptula et al. (44) showed no major complications using autologous fat grafting.

Lipofilling in clinical studies focusing on tenolysis

Regarding tenolysis with additional lipofilling, Damgaard et al. (66) reported a case where recurrent extensor tendons adhesions on a foot were successfully treated with tenolysis supplemented by autologous fat grafting; resulting in improved scar aspect and improved

function. Another case report by Colonna et al. (67) reports 3 cases of lipofilling in tendon scar treatment in two feet and one severely burned hand. Three sessions of lipofilling over 6 months resulted in improvement of flexion contracture, range of motion and hypoesthesia.

Recently, Cortes et al. (46) even demonstrated the efficacy of a minimally invasive tenolysis with lipofilling, resulting in improved postoperative TAM and improved pain scores in patients with stiff digits. In 11.8% of the 102 operated digits superficial infections were seen; and in only 1.9% of the tenolysed digits tendon ruptures and donor site pain was seen. Additionally, Deptula et al. (44) described a case of 60-year-old man presenting with a fixed PIP-joint flexion contracture of 110 degrees. The patient was treated with tenolysis in combination with autologous fat grafting, harvested from the abdomen. The patient achieved full passive range of motion and no complications at the 5-month postoperative follow-up.

6.4 Summary of known and potential risks and benefits

Lipofilling is generally considered a safe technique based on adequate patient safety and good effectiveness. However, like any surgical intervention, potential risks are present and a low rate of minor complications can occur (38-43, 46). Common limited side effects stated in the literature are edema, (abdominal) hematoma, seroma, infection treatable with antibiotics, contour deformity and paresthesia.

Fortunately, the complication rate with lipofilling is extremely low when compared to most open surgical methods. Moreover, the likelihood of complications decreases significantly with the surgeon’s experience.

An important feature for subcutaneous fat, is that it can easily be obtained by the minimally invasive procedure of liposuction. This procedure is well tolerated, safe, and low-cost. Till this date, only minor complications of lipoharvesting have been noticed when performing lipoharvesting: hematoma and/or swelling of the harvesting site, neuropraxia due to collision of the cannula against a sensible nerve and hypersensitivity of harvesting site.

6.5 Description and justification of route of administration and dosage

1ml of harvested autologous fat or 0.9% NaCl will be injected subcutaneous at the operation site after wound closure.

6.6 Dosages, dosage modifications and method of administration

Not applicable.

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable.

6.8 Drug accountability

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

7.1 Name and description of non-investigational product(s)

Not applicable.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Not applicable.

7.4 Summary of known and potential risks and benefits

Not applicable.

7.5 Description and justification of route of administration and dosage

Not applicable.

7.6 Dosages, dosage modifications and method of administration

Not applicable.

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

7.8 Drug accountability

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

TAM

TAM is described by the American Society for Surgery of the Hand (ASSH) as the sum of active MCP, PIP and DIP arc of motion in degrees of an individual digit (50, 51), of which the norm is 260 degrees. See for the assessment of this arc of motion in the alinea below.

8.1.2 Secondary study parameters/endpoints (if applicable)

AROM and PROM of the MCP-, PIP- and DIP-joint

The AROM and PROM of the MCP-, PIP- and DIP-joint are the arc of motion of the specific joint, which the patient can respectively actively move or can be passively moved by an outside force.

1. In case of ORIF, patients will be physically examined by the clinician preoperatively to assess the AROM and PROM of MCP-, PIP- and DIP-joint of the contralateral unaffected digit. In addition, patients will be physically examined by the hand therapist or clinician 6 weeks, 3 months and 6 months postoperatively to assess the AROM and PROM of MCP-, PIP- and DIP-joint of the operated digit and the contralateral unaffected digit (Figure 1A).
2. In case of tenolysis, patients will be physically examined by the hand therapist or clinician preoperatively and 6 weeks, 3 months and 6 months postoperatively to assess the AROM and PROM of MCP-, PIP- and DIP-joint of the affected/operated digit and the contralateral

unaffected digit (Figure 1B).
Measurements will be done using a goniometer.

Postoperative NRS-scores of the abdominal donor site

Patients will rate their postoperative pain on a NRS (0-10 scale) for the abdominal donor site on fixed time points: 2 weeks, 6 weeks, 3 months and 6 months postoperative (Figure 1A + B).

Postoperative MHQ-scores

1. In case of ORIF, patients will complete the MHQ-questionnaire (48, 49) on fixed time points: 6 weeks, 3 months and 6 months postoperative (Figure 1A).
2. In case of tenolysis, patients will complete the MHQ-questionnaire (48, 49) on fixed time points: preoperative and 6 weeks, 3 months and 6 months postoperative (Figure 1B).

Postoperative radiographic union outcomes

In case of ORIF, patients will undergo radiographic evaluation at 6 months postoperatively, during which the degree of radiographic union will be assessed. Conform regular protocol, a three-view radiographic examination (comprising of antero-posterior, oblique and lateral views) will be performed of the operated digit. The radiographic examination will be performed prior to the physical examination of AROM and PROM of the MCP-, PIP- and DIP-joint by the hand therapist or clinician. The radiographic evaluation will be performed by a radiologist, who will assess the degree of union. Given the postoperative time point, the degree of union will be categorized as union (complete healing with proper bone alignment and fusion), non-union (lack of healing, with no bridging of the fracture ends) or malunion (healing in an incorrect alignment or angulation, leading to deformity) (5).

Postoperative complications

Postoperative complications, including infection, wound-related problems and stiffness will be registered by the clinicians if a patient visits the outpatient clinic for this purpose during the 6 months postoperative period, independent of the fixed postoperative timepoints.

Secondary procedures

In case of ORIF, secondary procedures, including revision surgery and tenolysis, will be

registered by the clinicians if this is indicated for the included patient during the 6 months postoperative period, independent of the fixed postoperative timepoints.

8.1.3 Other study parameters (if applicable)

Not applicable.

8.2 Randomisation, blinding and treatment allocation

Patients will be randomized for perioperative lipofilling or NaCl-injection using a randomisation model in Research Electronic Data Capture (REDcap). This is a secure web-based software platform designed to support the data capture for studies, providing: an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages and procedures for data integration and interoperability with external sources (68, 69).

The allocation ratio will be 1:1. Permuted blocks will be used in the randomization list, this list will be coded and created by the REDcap administrator to ensure the researcher is unaware of the order. The operating plastic surgeons or residents will not be blinded to treatment allocation; patients, hand therapists and plastic surgeons or residents, who did not perform the surgery, will be blinded for treatment allocation. With regard to a double-blinded trial, the postoperative assessment will be fulfilled by the hand therapists and plastic surgeons or residents, who did not perform the surgery. The operating plastic surgeons or residents will be blinded for assessment of postoperative outcomes; patients, hand therapists and plastic surgeons or residents, who did not perform the surgery, will not be blinded.

Blinding may be broken in case of emergency during the study.

8.3 Study procedures

All tasks in the study procedures will be divided and recorded in a delegation log.

1. In case of ORIF, 56 patients will be included in this study (see “Chapter 4.4 Sample size calculation”); 28 patients will be included in both the lipofilling group and NaCl-injection group.
2. In case of tenolysis, 74 patients will be included in this study (see “Chapter 4.4 Sample size calculation”); 37 patients will be included in both the lipofilling group and NaCl-injection group.
The inclusion will take place by the clinicians at the outpatient clinic of the Plastic Surgery

Department of the Jeroen Bosch Hospital. See “Chapter 11.2 Recruitment and consent” for the inclusion procedure. Following the inclusion procedure, the patient will be randomized using the randomisation model in REDcap. The study number and randomised treatment option (lipofilling or NaCl-injection) will be written in the electronic medical chart. More information on the randomisation can be found under “Chapter 8.2 Randomisation, blinding and treatment allocation”. Moreover, the following information will be collected: patient information (email address, which is needed for sending the questionnaires by email); demographic parameters and disease characteristics. All characteristics mentioned will be written in the electronic medical chart using standardized formats.

Preoperative assessment

1. In case of ORIF, patients will preoperatively undergo a physical examination by one of the clinicians to assess the range of motion of the contralateral unaffected digit.
2. In case of tenolysis, patients will preoperatively undergo a physical examination by one of the clinicians or hand therapists (Hand Pols Expertise Centrum Jeroen Bosch Ziekenhuis) to assess the range of motion of the affected digit and the contralateral unaffected digit. Additionally, each patient will complete the Michigan Hand Outcomes Questionnaire (MHQ) (48, 49).

The Michigan Hand Outcomes Questionnaire is a patient-rated reliable and valid instrument for measuring hand outcomes (48, 49), focusing on the following domains: 1. overall hand function, 2. activities of daily living (ADL), 3. pain, 4. work performance, 5. aesthetics, and 6. patient satisfaction with hand function. The raw scale score for each of the six domains is the sum of the responses of each scale item. The raw scale score is converted to a score ranging from 0-100 using a scoring algorithm. The score for the affected hand is obtained by selecting either the right or the left hand score. The overall MHQ-score (0-100) can be obtained by summing the scores for all six domains after reversing the pain scale (pain=100-pain score) and then dividing by six. The higher the score, the better the hand outcomes.

The duration of the preoperative assessment is estimated at 15-45 minutes, which is conform the standard protocol/visit at the outpatient clinic.

Surgical procedure with perioperative lipofilling vs. NaCl-injection

The operative procedure of both ORIF and tenolysis will be performed conform regular protocol. This means that the desired urgency of ORIF of the P1 fracture is 1 week after initial trauma; for tenolysis the urgency is approximately 6 weeks after indicating the need for tenolysis based on a shared decision between patient, plastic surgeon and hand therapist. The

surgical treatment will be performed under local (in case of tenolysis), locoregional/plexus anesthesia or general anesthesia in consultation with both the patient and anesthesiologist.
In case of ORIF, the procedure will be conducted with the Mini Fragment System (Arthrex, Naples, FL, USA) under sterile conditions following standard protocols. The fracture site will be exposed through appropriate surgical access. Once visualized, the fracture will be anatomically reduced and temporarily stabilized to maintain alignment. An appropriate fixation plate will be selected based on the anatomical location and fracture configuration. If necessary, the plate will be shortened using the designated cutter, ensuring alignment with the size indicators on the clamp. If necessary, the plate can be contoured to the bone using threaded plate benders to ensure optimal fit. Temporary fixation of the plate will be achieved using clamps or BB-Taks. A bicortical hole will be drilled using the appropriate color-coded drill and calibrated drill guide. The drill guide will be used to determine the correct screw length and may also assist in the placement of independent lag screws. The plate will then be secured to the bone using the selected screws. If variable-angle locking (VAL) screw placement is required, VAL drill guides will be used to allow for up to 15° of off-axis locking. Screw insertion will follow the standard protocol as described above.
In each patient, 20ml of lipoaspirate will be manually harvested, under additional tumescent anesthesia (i.e. a very diluted solution of lidocaine, adrenaline and sodium bicarbonate) (58) of an area with a diameter of ca. 15cm, from the subdermal fat layer of the lower abdomen using very fine harvesting cannulas.
In case of lipofilling, the harvested autologous fat will be processed for injection by centrifugation and emulsification. 1ml of the harvested and processed autologous fat will be injected subcutaneous at the operation site after wound closure. With regard to the control group, only 1ml 0,9% NaCl will be injected subcutaneous at the operation site after wound closure. This procedure will take an additional 10 minutes of operation time.

Postoperative assessment

After a postoperative period of 6 weeks, 3 months and 6 months including competent hand therapy, each patient will undergo a physical examination by the hand therapist or clinician to assess the TAM and AROM and PROM of the MCP-, PIP- and DIP-joint of the operated digit and the contralateral unaffected digit. Additionally, patients will then complete the MHQ (Fig. 1A + B).
In addition, patients will rate their postoperative pain on a NRS (0-10 scale) for the abdominal donor site on fixed time points: 2 weeks, 6 weeks, 3 months and 6 months postoperative (Fig. 1A + B).
The Numeric Rating Scale (NRS) for pain (70) is a scale to assess pain severity at that moment

in time ranging from 0-10, with 0 meaning ‘no pain’ and 10 meaning ‘the worst pain imaginable’.
In case of ORIF, radiographic evaluation of the operated digit will be performed, according to the standard protocol, prior to the physical examination by the hand therapist or clinician to assess the degree of radiographic union (non-union, malunion, or union) at 6 months postoperative.
The duration of the postoperative assessment is estimated at 30-45 minutes per visit, which is conform the standard protocol/visit at the outpatient clinic.

In case patients do not fill in the pre- and/or postoperative questionnaires, they will be contacted by email and later by phone. In case a patient does not succeed in responding, they will be called and the researcher will fill in the questionnaires.

8.4 Withdrawal of individual subjects

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a patient from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Reasons for withdrawal are as follows:

- In case conversion is warranted;
- In case the patient wishes to withdraw him/herself;
- In case it is in the best interest of the patient that he/she is withdrawn;
- In case the patient is not comply with the rules of the study protocol, despite repetitive instructions and reminders.

8.5 Replacement of individual subjects after withdrawal

A dropout rate of 20% is assumed and therefore we will correct our sample size calculation (see “Chapter 4.4 Sample size calculation”). A dropout of 20% or more is common in evidence based medicine as shown in a previous review of randomised controlled trials in four top medical journals (71). However, a dropout rate of more than 20% could also seriously threat the validity of the data (72). Therefore, the rate of 20% is chosen to anticipate a possible level of dropouts, but also to ensure data integrity and validity.

8.6 Follow-up of subjects withdrawn from treatment

Active follow-up will be done with patients who withdrew from the study for a medical reason or an adverse event. No active follow-up will be done on withdrawn subjects with non-urgent/non-medical reasons other than the regular post-operative follow-up after ORIF or tenolysis.

8.7 Premature termination of the study

The criteria for terminating the study prematurely are:

- Risks for the safety of the patients;
- Extreme difficulties regarding the logistics of the study;
- In case the investigator/sponsor has valid arguments to terminate the study.

In case the study is ended prematurely this will be reported to the medical ethics assessment committee (METC), the monitor and the board of directors (RvB).

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to lipofilling. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded in detail.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- Results in death;
- Is life threatening (at the time of the event);
- Requires admission or prolongation of admission inevitable;
- Results in persistent or significant disability or incapacity;
- Is a congenital anamoly or birth defect;
- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs through the web portal *Onderzoeksportaal* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable. However, the study will be monitored. An initiation visitation will take place before inclusion of the first patient. This is essential to start the study. Following inclusion of 10% of the sample size, a next monitor visitation will be planned. Afterwards, the visitations will be planned if deemed necessary. When the study ends, the close out visitation will take place.

10. STATISTICAL ANALYSIS

10.1 Primary and secondary study parameter(s)

Both primary and secondary outcomes will be represented as continuous variables; except for radiographic union outcomes, postoperative complications and secondary procedures. Due to linear regression, normality will be checked by comparing the distribution of the residuals to a normal distribution based on visually inspecting the Q-Q plot. Comparative analyses between the two groups (lipofilling vs. control) will be conducted at three time points: 6 weeks, 3 months, and 6 months. Only in case of the secondary outcome NRS-score of the abdominal donor site, the comparative analysis will also be conducted at an additional time point of 2 weeks. This examination will employ mixed model linear regression, with each participant's time points considered the lowest level, and the participant assigned to the level above. To address the longitudinal nature of the study, a random intercept and slope will be incrementally incorporated. The final model is the combination of the simplest possible with the lowest -2log Likelihood. A Time*Group interaction term will be introduced to assess potential group differences over the course of time. Statistical significance will be determined at the conventional threshold of $p < 0.05$, using the Likelihood Ratio Test.

These analyses will be performed separately for patients undergoing ORIF after P1 fractures and those undergoing tenolysis after operative treatment of P1 fractures.

Radiographic union outcomes, postoperative complications and secondary procedures
These secondary outcomes, including radiographic union outcomes at 6 months postoperative and postoperative complications (including infection, wound-related problems and stiffness) and secondary procedures (including revision surgery and tenolysis) during the 6 months postoperative period, will be discrete variables. These data will be analyzed using descriptive statistics.

In case of dropouts, reasons will be registered and reported in the results.

10.2 Other study parameters

Not applicable.

10.3 Interim analysis (if applicable)

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study follows the principles of the Declaration of Helsinki, 64th World Medical Association (WMA) General Assembly, October 2013 and is in accordance with the Medical Research Involving Human Subjects Act (WMO), Medical Treatment Agreements Act (WGBO) and General Data Protection Regulation (AVG). This study is designed and will be performed in accordance with Good Clinical Practice (GCP) and the Directive Quality Assurance Human bound Research by the Dutch Federation of University Medical Centers (NFU).

11.2 Recruitment and consent

Recruitment will take place by the clinicians at the outpatient clinic of the Plastic Surgery Department of the Jeroen Bosch Hospital. Patients consult the clinicians due to:

1. A single radiologically proven P1 fracture of digit 2-5 with an indication for ORIF, or;
2. Limited digital function after operative treatment of a P1 fracture with an indication for tenolysis.

Both male and female patients in the age 18-65, who are eligible after screening against the eligibility criteria, will be informed by the clinicians about the existence of the study. Patients will be asked by their clinician if they are interested in reading the PIF of the study, with all its benefits, minor risks and consequences. In addition, they will be told they are free to decline participation; this does not affect their treatment. If patients wish to leave the study later on, they are free to do so at any time. The PIF with all relevant points of the study and the ICF will be handed over to the patient by their clinician. A box will be placed at the front office of the outpatient clinic, in which the last version of the PIF and ICF will be present. This box will be

checked monthly for quantity. Thereafter, a 2-day or 14-day period is given for consideration, respectively for ORIF and tenolysis. This 2-day period deviates from the recommended 14-day period due to the procedural need for surgical repair within 1 week after trauma, with the fracture being operated on at the earliest 2 days after visiting the outpatient clinic. Throughout the information and consideration period patients are always able to ask the investigators and even an independent expert for additional information to be informed optimally; which is also stated in the PIF. After the aforementioned consideration period, patients will be contacted telephonically by the investigators, clinicians or by the Plastic Surgery Department secretary to ask if a decision was made. If the patient decides to participate, the patient will be asked to sign the ICF on the day of operation with presence of one of the clinicians. If not, the patient will be automatically denied from enrolling in the study. Participating patients will receive a copy and the ICF will be put in the electronic medical chart. This will be overseen by one of the secretaries at the department. After putting the ICF in the electronic medical chart, it will be placed in the trial master file (TMF). The TMF will be kept in a closet at the secretary office. The patients' General Practitioner will be notified by letter after enrolment into the study.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

The use of lipofilling may hold many future applications in (posttraumatic) hand surgery, which has already been suggested by previous studies (43-46). The results of this study will provide us with new insights in the possibility of the use of lipofilling or its substances in the surgical treatment of hand traumas, especially regarding fractures and tenolysis. This could possibly result in an improvement of (postoperative) range of motion and prevent secondary surgery.

Potential risk of any adverse events for the included patient is extremely low. Lipofilling is generally considered a safe technique based on adequate patient safety and good effectiveness. However, like any surgical intervention, potential risks are present and a low rate of minor complications can occur (38-43, 46). Common limited side effects stated in the literature are edema, (abdominal) hematoma, seroma, infection treatable with antibiotics, contour deformity and paresthesia. Fortunately, the complication rate with lipofilling is extremely low when compared to most open surgical methods. Moreover, the likelihood of complications decreases significantly with the surgeon's experience.

An important feature for subcutaneous fat, is that it can easily be obtained by the minimally invasive procedure of liposuction. This procedure is well tolerated, safe, and low-cost. Till this date, only minor complications of lipoharvesting have been noticed when performing lipoharvesting: swelling of the harvesting site, neuropraxia due to collision of the cannula against a sensible nerve and hypersensitivity of harvesting site.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data collection will be performed by the researcher BDV using REDcap (68, 69) as mentioned under “Chapter 8.2 Randomisation, blinding and treatment allocation”. This is a secure web-based software platform. Patients will be randomized and receive a study number allocated by REDcap. This number is written in the patient’s electronic medical chart. The researcher BDV, VDH and the monitor will have access to REDcap and source data.

The only information stored in REDcap that can be traced back to the patient is the email address, this is needed to send the questionnaires to the participants. The rest of the data collection will be anonymous. In addition, in the randomisation module arm the patient’s email address will be collected, whereas in the individual study arms (lipofilling and NaCl-injection), all information will be anonymous.

Key documents will be kept in Research Manager and the Trial Master File. The data will be

stored for 15 years after the study has ended.

12.2 Monitoring and Quality Assurance

As mentioned under “Chapter 9.5 Data Safety Monitoring Board (DSMB)/Safety Committee” the study will be monitored by monitors at the Jeroen Bosch Hospital. An initiation visitation will take place before inclusion of the first patient. This is essential to start the study. Following inclusion of 10% of the sample size, a next monitor visitation will be planned. Afterwards, the visitations will be planned if deemed necessary. When the study ends, the close out visitation will take place.

The following characteristics will be monitored: Trial Master File (TMF) and Investigator Site File (ISF), inclusion, informed consent procedures, source data verification, study team, authority, data safety, S(AE)’s and study procedures.

12.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial;
- The scientific value of the trial;
- The conduct or management of the trial; or
- The quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited

METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

The trial will be registered with an accredited trial register. The results of the study will be published in scientific papers. The information in the papers will be anonymous. The investigator and researcher declare there is no conflict of interest with respect to the protocol, authorship and future publication of scientific articles.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

A summary of the most important mechanisms in animal and clinical studies can be found in "Chapter 6 Investigational product".

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

In “Chapter 6 Investigational product” an extensive summary of clinical evidence of human beings exposed to products with similar biological mechanisms (lipofilling) can be found.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable.

e. Analysis of potential effect

Not applicable.

f. Pharmacokinetic considerations

Not applicable.

g. Study population

The study population consists of relatively healthy male and female patients. Pregnant women and women with an active child wish will be excluded from the study.

h. Interaction with other products

Not applicable.

i. Predictability of effect

Not applicable.

j. Can effects be managed?

Effects cannot be managed.

13.2 Synthesis

To reduce the risk we have taken some measures. Firstly, the following exclusion criteria are established:
1. Pregnant patients and patients with an active child wish will be excluded. It is unknown whether lipofilling will have any effect on a pregnant woman or child during a pregnancy.
2. Patients with a known systemic disease and/or treatment with prednisone, immunotherapy or hormone therapy will be excluded.

Secondly, patients will only receive lipofilling or NaCl-infiltration around the operation site at the end of the ORIF or tenolysis. Thus, the exposed area will be really small; like the length of the proximal phalanx. Furthermore, the area of lipoharvesting will be as small as possible to harvest an adequate amount of 20ml of lipoaspirate, under local anesthesia, resulting in an estimated area with a diameter of ca. 15cm. However, there still remain some risks regarding the lipoharvesting procedure (see “Chapter 6.4 Summary of known and potential risks and benefits”). Nevertheless, these risks are dependent on the size of the lipoharvesting area, which in our study is really small, and plastic surgeons having experience with lipoharvesting will perform the procedure to minimize the risk. Overall, the potential risk of lipofilling in scar-related conditions and hand surgery is extremely low. Lipofilling is generally considered a safe technique based on adequate patient safety and good effectiveness. However, like any surgical intervention, potential risks are present and a low rate of minor complications can occur (38-43, 46; see “Chapter 6.4 Summary of known and potential risks and benefits”).

Thirdly, the duration of the follow-up will be set on 6 months with three physical follow-up moments. During these follow-up moments patients will complete the MHQ and give an NRS-score. Additionally, they will undergo a physical examination by an experienced hand therapist or clinician to assess the TAM and AROM/PROM of the MCP-, PIP- and DIP-joint of the operated digit. In case of ORIF, radiographic evaluation of the operated digit will be performed 6 months postoperatively, prior to the physical examination, to assess radiographic union outcomes. The duration of the postoperative assessment will only last an estimated 30-45 minutes.

The remaining risks in this trial are acceptable because of the scientific value of the results of this study. This model will give us information about the possibility of the use of lipofilling or its substances in the surgical treatment of hand traumas, especially regarding fractures and tenolysis. This could possibly result in an improvement of (postoperative) range of motion and

prevent secondary surgery.

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