Trials

STUDY PROTOCOL

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Limited fasciectomy with versus without autologous adipose tissue grafting for treatment of Dupuytren's contracture (REMEDY): study protocol for a multicentre randomised controlled trial

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Abstract

Background Dupuytren's contracture is a hereditary disorder which causes progressive fibrosis of the palmar aponeurosis of the hand, resulting in digital flexion contractures of the affected rays. Limited fasciectomy is a standard surgical treatment for Dupuytren's, and the one with the lowest recurrence rate; however, the recurrence is still relatively high (2–39%). Adipose-derived stem cells have been shown to inhibit Dupuytren's myofibroblasts proliferation and contractility in vitro, as well as to improve scar quality and skin regeneration in different types of surgeries. Autologous adipose tissue grafting has already been investigated as an adjuvant treatment to percutaneous needle fasciotomy for Dupuytren's contracture with good results, but it was only recently associated with limited fasciectomy. The purpose of REMEDY trial is to investigate if limited fasciectomy with autologous adipose tissue grafting would decrease recurrence compared to limited fasciectomy alone.

Methods The REMEDY trial is a multi-centre open-label randomised controlled trial (RCT) with 1:1 allocation ratio. Participants ($n=150$) will be randomised into two groups, limited fasciectomy with autologous adipose tissue grafting versus limited fasciectomy alone. The primary outcome is the recurrence of Dupuytren's contracture on any of the treated rays at 2 years postoperatively. The secondary outcomes are recurrence at 3 and 5 years, scar quality, complications, occurrence of algodystrophy (complex regional pain syndrome), patient-reported hand function, and hypodermal adipose tissue loss at 1 year postoperatively in a small subset of patients.

Discussion The REMEDY trial is one of the first studies investigating limited fasciectomy associated with autologous adipose tissue grafting for Dupuytren's contracture, and, to our knowledge, the first one investigating long-term outcomes of this treatment. It will provide insight into possible benefits of combining adipose tissue grafting with limited fasciectomy, such as lower recurrence rate and improvement of scar quality.

Trial registration ClinicalTrials.gov NCT05067764, June 13, 2022.

Keywords Dupuytren, Recurrence, Fasciectomy, Aponeurectomy, Adipose tissue graft, Fat graft, Lipofilling

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Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Limited fasciectomy with versus without autologous adipose tissue grafting for treatment of Dupuytren's contracture (REMEDY): study protocol for a multicentre randomized controlled trial.
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Name and contact information for the trial sponsor {5b}	Hôpital Privé Saint Martin ELSAN 56 Allée des Tulipes 33600 Pessac France
Role of sponsor {5c}	Finance of services inherent to the research (methodology, ethical and regulatory submission, database, and medical writing).

Introduction

Background and rationale {6a}

Dupuytren's disease is a common hereditary disorder (between 1 and 31% in Western population [1]), affecting the palmar aponeurosis of the hand. A progressive contractile fibrosis adheres to the skin and the phalanges, eliminating the space for the hypodermal adipose tissue and gradually bending the affected rays with the consequence of significant functional impotence. Various medical and surgical treatments are available, including Clostridium histolyticum collagenase injections (CCH), percutaneous needle fasciotomy (PNF) and limited fasciectomy (LF). Currently, none of these treatments allows to diminish frequent recurrences (CCH 6.8–80% [2–6], PNF 46–84.9% [2, 4, 7], LF 2.3–39% [3, 5–9]) [2–9]. Furthermore, skin atrophy and fibrous appearance of scars in the treated areas remain an unresolved problem, present in all the treatments mentioned above [10].

For more than 40 years, plastic and reconstructive surgeons have been able to build extensive experience in the field of autologous adipocyte transplants by liposuction (from abdominal adipose tissue, lower limbs, etc.) and reinjection into sites with volume deficit. Initially designed for volume filling purposes (aging face, drug-induced lipodystrophy, post-traumatic, etc.), "lipofilling" proved to be regenerative: the treated sites showed improved tissue quality, particularly in terms of flexibility and vascularisation, both in clinical [11, 12] and animal [13] studies. This effect can be explained by presence in human lipoaspirate of mesenchymal stem cells from adipose tissue (adipose-derived stem cells [ADCs]) which are capable of differentiation towards several tissue lineages [14]. In vitro experiments have been able to demonstrate an inhibitory effect of ADCs on the myofibroblasts responsible for formation of contractile cords in Dupuytren's disease [15, 16]. These findings were already used in clinical practice by combining the autologous adipose tissue grafting with percutaneous aponeurotomy and lipofilling (PALF) for Dupuytren's contracture (PALF) [17–20]. Despite excellent results in the short and medium term and improvement of skin quality in areas of fibrosis, PALF did not reduce long-term recurrence [9] which is significantly higher than for open surgical treatment by limited fasciectomy [7, 9, 21]. It might be due to remaining fibrous cords, which are only sectioned but not removed in percutaneous needle aponeurotomy. Hence, the inhibitory potential of the ADCs provided by the injected adipose tissue could be exceeded by the volume of the cords already formed.

In this context, we hypothesise that combining limited fasciectomy and autologous adipose tissue grafting could reduce recurrence rate, as well as improve scar quality. We first conducted a clinical feasibility and safety study

for this new treatment, including 70 patients between 2012 and 2017 [22], with good results. The only other published study on limited fasciectomy with autologous adipose tissue grafting [23] showed worse functional outcomes and more complications than limited fasciectomy alone. However, this was a small study (45 patients randomised 1:1) with 1 year follow-up. We are planning to address these limitations in REMEDY trial by including larger number of patients and ensuring the follow-up of 5 years.

Objectives {7}

To evaluate outcomes of limited fasciectomy with autologous adipose tissue grafting (experimental group) versus limited fasciectomy alone (control group) for treatment of Dupuytren's contracture:

(1) To evaluate recurrence rates, as defined by Kan et al. and Felici et al. [24–26]: contracture > 20° compared to 6 weeks postoperatively, in presence of palpable cord, on any operated joint.
(2) To evaluate scar quality, complications, occurrence of algodystrophy (complex regional pain syndrome), hand function.

Trial design {8}

This is a pragmatic, two-arm parallel-group, multicentre, evaluator-blinded randomised-controlled trial (RCT) in a superiority framework with 1:1 allocation ratio. If during the trial, the second hand requires surgery after the patient has undergone surgery on the first hand, it will receive the other intervention from the two available in the trial, to perform a within-subject comparison between the interventions.

A total of seven surgeons from two centres will perform either intervention (limited fasciectomy with or without autologous adipose tissue grafting).

Methods: participants, interventions and outcomes

Study setting {9}

The study is based in two hand units of private hospitals in France:

(1) Hôpital Privé Saint Martin, Institut Aquitain de la Main, Elsan Group, Allée des Tulipes, 33600 Pessac, France (the coordinating centre)
(2) Clinique Privée Santé Atlantique, Institut de la Main, Elsan Group, Avenue Claude Bernard, 44800 Saint-Herblain, France.

Eligibility criteria {10}

A total of 150 patients undergoing limited fasciectomy for Dupuytren's contracture will be enrolled.

The inclusion criteria will be:

(1) Men and women aged 18 years or over
(2) Dupuytren's with a contracture of II-IV Tubiana stage [27] in either joint
(3) Indication for limited fasciectomy
(4) "Skin pinch" of > 1 cm on the posterior part of the arm
(5) Affiliation to social security scheme
(6) Signature of informed consent prior to any study-related procedures
(7) Ability to answer questionnaires and to communicate freely in French.

The exclusion criteria will be:

(1) History of any surgical treatment, radiotherapy or collagenase injections for Dupuytren's contracture
(2) Dupuytren's contracture of thumb only
(3) Indication for full-thickness skin graft or island pedicle flap
(4) Active autoimmune disease
(5) Any other significant disease or disorder which, in the opinion of the investigating surgeon, may put the participant at risk because of participation in the study, or may influence the result of the study
(6) Pregnant or breastfeeding women
(7) Adult under guardianship, curatorship, or other legal protection

Who will take informed consent? {26a}

Patients with Dupuytren's contracture and requiring surgical treatment will be evaluated by an investigating surgeon. During consultation of the patient and after assessing the eligibility, the patient will be offered to enrol in the current study and will receive an explanation of the study.

An information note, as well as consent form will be provided by the investigating surgeon. The patient will be granted a period of reflection. The informed consent will be collected during the standard anaesthesia consultation.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This trial does not involve collecting biological specimens for storage.

Interventions

Explanation for the choice of comparators {6b}

Autologous adipose tissue grafting in association with limited fasciectomy (experimental group) and limited

fasciectomy alone (control group) were identified as comparators. Limited fasciectomy is a standard surgical treatment for Dupuytren's contracture. Autologous adipose tissue grafting has been well investigated as an adjunct treatment to percutaneous needle fasciotomy for Dupuytren's contracture [9, 17–20]. However, it has only recently been used during limited fasciectomy [23] and the evidence for the combined treatment are still limited.

Intervention description {11a}

During one surgery (both in experimental and control group), more than one ray can be treated simultaneously.

Limited fasciectomy (control)

Standard limited fasciectomy is performed on the patient in supine position, under regional anaesthesia by axillary block, using tourniquet inflated to 250 mmHg. Bruner incisions [28] are made, skin flaps are elevated, and the excision of the fibrous cords and nodules is performed, as complete as possible. Skin is closed with any of the following methods, depending on the region and wound size: direct suture, local cutaneous-adipose tissue flap, or secondary healing.

Autologous adipose tissue grafting (experimental)

Autologous adipose tissue grafting is performed in the experimental group using St'rim™ adipose tissue grafting system, and approximately 10 ml of adipose tissue is harvested by skin punctures of the posterior, medial and/or anterior aspects of the arm, depending on the yield. Limited fasciectomy is performed the same way in both groups. After conditioning and sedimentation and following the skin closure on the limited fasciectomy site, the adipose tissue graft is injected through the Bruner incisions [28], where skin closure was possible, approximately 2 ml per treated ray.

Criteria for discontinuing or modifying allocated interventions {11b}

Both interventions are a one-stage surgical treatment; hence, their discontinuation is not possible, once delivered. However, the participation in the study can be interrupted at any time:

(1) By a patient wishing to withdraw from the study, without any justification necessary,
(2) By an investigating surgeon, if they judge that a permanent or temporary interruption would serve the best interests of a patient, especially in case of a serious adverse event (SAE).

In these cases, data already collected will be kept and analysed unless the patient explicitly demands for their data to be deleted from the database. No further data will be collected for these patients, and they will continue to receive medical care according to usual practices of the investigating centre.

Strategies to improve adherence to interventions {11c}

There is no specific strategy implemented to improve adherence, given that both interventions are one-stage surgeries rather than a series of steps that requires adherence.

Relevant concomitant care permitted or prohibited during the trial {11d}

Patients will not be required to interrupt their usual medical treatment during the trial. If any of the treatments should be interrupted before surgery (e.g. anticoagulants), the patient will be informed by the investigating surgeon, as in usual practice.

Provisions for post-trial care {30}

There is no specific post-trial care. After the end of the trial, the patients will continue their routine care by primary care physicians.

Outcomes {12}

Primary outcome of this trial is recurrence, as defined by Kan et al. and Felici et al. [24–26], at 2 years postoperatively: contracture >20° compared to 6 weeks postoperatively, in presence of palpable cord, on any operated joint. The clinical evaluation will be performed by the investigating surgeon.

Secondary outcomes of this trial will be:

(1) Recurrence (defined above) at 3 and 5 years postoperatively.
(2) Scar quality and appearance, assessed with the Patient and Observer Scar Assessment Scale (POSAS) at 1 and 2 years postoperatively. POSAS is a validated questionnaire which consists of 2 separate scales of 6 items each (a scale for the observer and a scale for the patient). Each item is evaluated on 10 points, from 1 (normal skin) to 10 (the worst scar), with the total score for each scale ranging from 6 to 60.
(3) Complications (surgical site infection, hematoma necessitating drainage, graft lysis due to adipose tissue necrosis, skin necrosis, skin depression of the aspiration site, nerve injury, tendon injury, ischemia due to vascular injury, digital necrosis, algodystrophy [complex regional pain syndrome], delayed healing, pathological scar, neuropathic pain), at 1 and 6 weeks postoperatively.

(4) Occurrence of algodystrophy (adverse event of special interest) at 1, 2, 3, and 5 years postoperatively. The diagnosis of algodystrophy will be based on Budapest criteria [29].
(5) Hand function, assessed with the Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaire preoperatively and at 6 weeks, 1, 2, and 5 years post-operatively. QuickDASH is a validated score, consisting of 11 questions, assessing the ability to perform daily activities including upper extremity. The final score ranges from 0 (normal function) to 100 (almost no function).

The patient will fill out the POSAS (patient-reported part) questionnaire and the QuickDASH questionnaire individually, without presence of the investigating surgeon, to decrease the risk of surgeon's influence on the outcomes.

Participant timeline {13}

The eligibility criteria will be verified during the inclusion visit (equivalent to first surgical consultation). Eligible patients will receive an information note, as well as consent form, which will be collected after the inclusion visit but before intervention. Depending on patient's preferences, organisational options and disease progression, the time interval between inclusion and intervention could range from 0 (inclusion and intervention on the same day) up to 6 months. The patients giving their informed consent for participation in the study will be randomised and will preoperatively complete the QuickDASH questionnaire.

Patient's participation will be approximately 5 years (Table 1) from the intervention to the final follow-up. Apart from the 3-year follow-up, which consists of a phone call, all the postoperative evaluations will be carried out by the investigating surgeons during on-site consultations. If a second surgery occurs after 3 years postoperatively, follow-up of the patient will be extended by 2 years in order to evaluate the recurrence of Dupuytren's contracture up to 2 years postoperatively.

Sample size {14}

The main criterion of the study is the recurrence at 2 years postoperatively. According to the literature, the expected recurrence rate for limited fasciectomy is 30% [3, 9], and we hypothesise that the adipose tissue grafting will improve this proportion by 20% (10% expected recurrence rate). Therefore, 69 patients per group (a total of 138) are needed to detect a statistically significant difference in the recurrence rate, using a Fisher exact test with a power of 80% and a two-tailed α of 5%. Assuming a 2-year loss to follow-up rate of 20% (based on the investigators experience), the total number of patients to be included will be 172 (86 per group).

Recruitment {15}

Patients with Dupuytren's disease of at least one ray and requiring surgical treatment will be seen in consultation by an investigating surgeon in one of the two participating centres and will be offered participation in the study if eligibility criteria are satisfied. The recruitment period is estimated to be 36 months.

Table 1 Timeline

	Inclusion visit (V-1)[a]	Intervention (V0)[a]	1 week follow-up (V1)	6 weeks follow-up (V2)	1 year follow-up (V3)	2 years follow-up (V4)	3 years follow-up (V5)[c]	5 years follow-up (V6)
Timeline	**D0: -30 to 0 weeks[a]**	**D0**	**D0 + 1 week**	**D0 + 6 weeks ± 2 days**	**D0 + 52 weeks ± 2**	**D0 + 104 weeks ± 2**	**D0 + 156 weeks ± 2**	**D0 + 260 weeks ± 2**
Demographic data	X							
Medical history	X							
Goniometry and cords palpation	X		X	X	X	X	X[c]	X
Eligibility assessment	X							
Informed consent	X[b]							
Randomisation	X[b]							
Allocated intervention		X						
POSAS questionnaire					X	X		
QuickDASH questionnaire	Preoperative			X	X	X		X
Complications		X	X	X				
Algodystrophy					X	X	X	X

[a] Inclusion visit and intervention can take place on the same day

[b] Collection of the consent form and subsequent randomisation take place after the inclusion visit, but before the intervention

[c] Follow-up call. If a patient describes recurrence symptoms during the call, a consultation with an investigating surgeon will be organised, and the goniometry and cords palpation will be performed

Assignment of interventions: allocation

Sequence generation {16a}

Randomisation with blocks of variable size will be used, stratified by the investigating surgeon (there will be seven randomisation sequences, one for each surgeon participating in the study). The randomisation sequences will be generated before commencement of the study separately for each stratum using WebSurvey software.

Concealment mechanism {16b}

The randomisation sequences will be concealed from staff as well as patients.

Implementation {16c}

The trial statistician will generate randomisation sequences for each stratum. The patient will be randomised to a treatment arm only after inclusion, and the allocation will be based on a unique number from the randomisation sequence, attributed to the patient's electronic case report form (eCRF), which is only accessible by the study staff.

Assignment of interventions: blinding

Who will be blinded {17a}

The nature of the interventions does not allow to blind neither the patient, nor the operating surgeon. The evaluators of all outcomes collected after day 45 (other hand surgeons or hand therapists) will be blinded. The choice of the 45 days timepoint allows the operating surgeon to perform the standard postoperative follow-up for their patients and collect the data on complications, as well as baseline goniometry at 6 weeks postoperatively.

Procedure for unblinding if needed {17b}

Unblinding will not occur in any circumstances.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The following information will be collected and included on the eCRF after enrolment and allocation:

(1) Patients' characteristics: age (years), sex, relevant medical and surgical history.
(2) Indication: side, affected rays, preoperative goniometry, cords palpation.
(3) Surgical parameters: type of wound closure.
(4) Clinical outcomes: complications, adverse events, occurrence of algodystrophy, postoperative goniometry, cords palpation, scar quality (POSAS questionnaire), hand function (QuickDASH questionnaire).

Plans to promote participant retention and complete follow-up {18b}

There is no specific strategy implemented in order to promote participant retention; however, losses to follow-up will be minimised as patients will return to the investigating centres to participate in physiotherapy sessions.

Data management {19}

All data will be stored and handled in accordance with data protection principles. Collected data must be entered by the principal investigator of the centre, or by any designated member of his team to whom this responsibility has been delegated. Each eCRF user will have their personal identifier and secure password to connect, enter and correct study data. Each access to the eCRF or modification of the data entered is electronically recorded and traced (audit trail). The data entered must be accurate and complete and will be checked and validated according to the sponsor's standard procedures. Automatic consistency checks, in addition to manual checks, will ensure data consistency and detect aberrant, missing or erroneous data. If necessary, requests for data corrections will be sent to the investigating centre. When all data is entered, checked and validated, and when no correction requests are pending, the principal investigator connects to the eCRF and validates the data by electronically signing the eCRF of each included patient.

Confidentiality {27}

In accordance with the legal provisions in force (articles L.1121–3 and R.5121–13 of the Public Health Code [PHC]), persons having direct access to the source data will take all the necessary precautions to ensure the confidentiality of the information relating to research procedures and to the participating patients, in particular with regard to their identity as well as to the results obtained. These persons, like the investigating surgeons themselves, are subject to professional secrecy. During the study, the collected data will be anonymised. Under no circumstances should the data clearly show the names, addresses or any directly identifiable information of the patients concerned. The sponsor will ensure that each participating patient has given their written consent for access to the individual data concerning them, which is strictly necessary for the quality control of the study.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable as no biological samples will be collected for this trial or future analysis.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The following datasets will be defined:

(1) Randomisation Set (RS) will include all randomised patients.
(2) Safety Set (SS) will include all randomised patients who underwent their assigned intervention.
(3) Full Analysis Set (FAS) will include all randomised patients who underwent their assigned intervention with at least one year of follow-up.
(4) Per Protocol (PP) will include all patients in the FAS population without major deviations from the protocol (deviations that could impact the assessment of the primary outcome).

All data will be presented by group (limited fasciectomy with versus without autologous adipose tissue grafting). Categorical variables will be described by number of observations, number of missing data, frequency and percentage of each modality. Continuous variables will be described by number of observations, number of missing data, mean, standard deviation, median, minimum and maximum. Inferential statistical tests will be carried out bilaterally with the type I error (α) set at 5% and confidence intervals (CIs) at 95%. Type I error will be minimised by applying Bonferroni correction to the entire analysis. In the event of a patient being operated on their second hand during the trial, the second hand will only be included in the supplementary analysis.

The primary outcome (recurrence at 2 years postoperatively) will be analysed on SS dataset, using the generalised estimating equations (GEE) model including the fixed factors: group, occurrence of algodystrophy, the Tubiana classification, the operator and the operator*group interaction. The main analysis will assume that all dropouts had a recurrence. A sensitivity analysis will be carried out on SS patients assuming that none of the dropouts had a recurrence. A confirmatory analysis will be carried out on the PP set.

The recurrence will be evaluated again on the remaining patients at 3 years and 5 years, according to the same model as for the primary outcome. The quality of scars will be assessed with the POSAS questionnaire at 1 and 2 years postoperatively, and analysed using a mixed model for repeated measures on the FAS dataset, including the following factors: the group as an explanatory variable and the occurrence of algodystrophy, the Tubiana classification, the type of wound closure, the operator, the time as repeated factor, the operator*group and time*group interactions and the POSAS questionnaire at 1 year as covariate. Hand function will be assessed with the QuickDASH questionnaire at 1, 2 and 5 years postoperatively and analysed by comparing between the two groups the percentage of patients having reached the minimal clinically important improvement (MCII), defined by an improvement of 8 points [30]. This comparison will be carried out using a logistic regression adjusted for the occurrence of algodystrophy, the operator, the operator*group interaction and the time effect. The complications (considered as a binary variable "yes/no" and considered positive after the first occurrence in a patient) and the occurrence of algodystrophy (considered as a binary variable "yes/no" and considered positive after the first occurrence in a patient) will be presented descriptively in the two groups, at each measurement time, on the SS dataset and compared using a chi-square test or an exact Fisher test according to the validity condition of chi-square test.

Interim analyses {21b}

No interim analyses are planned. Given that both limited fasciectomy and autologous adipose tissue grafting are validated in clinical practice and in the literature, there is no reason to anticipate exceptionally poor outcomes or unexpected complications. Furthermore, reaching a statistically significant difference between the groups before the planned end of the study is unlikely with the anticipated cohort size.

Methods for additional analyses (e.g. subgroup analyses) {20b}

If any patients from the FAS dataset get operated on their second hand during the trial, they would be included in a supplementary analysis, where both hands would be analysed for the primary outcome (recurrence at 2 years postoperatively) using the GEE model including the fixed factors: group, occurrence of algodystrophy, the Tubiana classification, the operator, the operator*group interaction, within-subject factor.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

For the primary outcome, two sensitivity analyses will be carried out on FAS patients with missing data, one by replacing them with a recurrence, the other by replacing them with an absence of recurrence. Missing data on other outcomes will not be replaced.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

Apart from the publication of the English version of the protocol, dataset and statistical code will not be made publicly available.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The research will be regulated by the standard operating procedures of Cellule Recherche Clinique Nouvelle Aquitaine ELSAN under supervision of the main author (Dr Elias T. Sawaya). The Cellule Nouvelle Aquitaine is created by the trial sponsor and is responsible for providing centralised monitoring of the study, in accordance with Good Clinical Practices (I.C.H. version 4 of May 1, 1996, and decision of November 24, 2006). The Cellule is composed of scientific director (medical coordination, scientific advisor), clinical study coordinator (planning, management, monitoring, and study coordination) and clinical research associate (CRA) (patient monitoring, data entering). There is a weekly exchange of information between the CRA and the clinical study coordinator. In case of any doubt or disagreement, the scientific director is consulted.

Composition of the data monitoring committee, its role and reporting structure {21a}

There will be no data monitoring committee, as this is a category 2 study (article L1121-1 of the PHC: interventional research on human subjects, involving only minimal risks and constraints), which corresponds to research evaluating usual care, hence, not anticipating new adverse events, overwhelming benefit, nor futility.

Adverse event reporting and harms {22}

Adverse event (AE) is defined in the article R.1123–39 of the PHC as any harmful manifestation occurring in a person who undergoes biomedical research, regardless if this manifestation is linked to the research or to the product on which this research relates.

SAE is defined in the same legal article as any AE that:

- Leads to death,
- Endangers the life of the patient,
- Requires hospitalisation or extension of hospitalisation,
- Causes a significant or lasting incapacity or handicap,
- Results in a congenital anomaly or malformation,
- Or any event considered medically serious.

Unexpected adverse event (UAE) is defined in the same article and concerns the research involving health products. It is any undesirable effect of the product whose nature, severity or evolution does not match the information given in the instruction manual or user manual.

The investigating surgeon must assess each AE and record it in the observation notebook, describing a diagnosis, a start date, severity of symptoms, administered treatment, measures taken in relation to the study procedure, as well as the link of causality between the study procedure and the AE. The investigating surgeon must notify the trial sponsor without delay about any SAE. The patient must be followed until the resolution of SAE even if they are withdrawn from the study. If the SAE is likely to be due to the treatment or study procedure, there is no limitation on the duration of the patient's follow-up.

The trial sponsor is responsible for the ongoing evaluation of the safety of procedure being the subject of the trial. They must assess:

- The causal link between the SAE and the research procedure.
- The expected or unexpected nature of the AE.

In the context of a category 2 study (PHC article L1121.1: interventional research on human subjects, involving only minimal risks and constraints) the implementation of specific vigilance (such as vigilance unit, safety committee) is not necessary. The occurrence of an unexpected SAE or an UAE will follow the usual vigilance process with the Regional Pharmacovigilance Centres or the National Agency for the Safety of Medicines and Health Products depending on the nature of the AE.

The expected AEs related to the interventions are as follows:

- Surgical site infection: adipose tissue donor site or operated ray.
- Collected hematoma requiring drainage: adipose tissue donor site or operated ray.
- Adipose tissue necrosis: operated ray.
- Skin necrosis: operated ray.
- Skin depression: adipose tissue donor site (too strong adipose tissue aspiration during harvesting).
- Nerve injury: operated ray (neuropraxia, axonotmesis or neurotmesis).
- Tendon injury: operated ray.
- Delayed healing (without infection): operated ray.
- Finger ischemia (due to vascular injury): operated ray.
- Algodystrophy (complex regional pain syndrome): operated limb.
- Pathological scar: operated ray.
- Neuropathic pain or paraesthesia: adipose tissue donor site or operated ray.

Frequency and plans for auditing trial conduct {23}

The CRA mandated by the sponsor will visit the investigation centres on a regular basis: to set up the study, during the study depending on the rhythm of inclusions

and patient monitoring schedule, and at the end of the study. During these visits, the following points may be reviewed:

- The presence of a copy of the informed consent, completed and signed,
- Compliance with the study protocol and the procedures defined therein,
- The quality of source documents and comparison with the data reported in the eCRF to check their accuracy and consistency.

The closing visit of the centres will be carried out by the CRA following the promoter's current procedures. The centres will be closed once the source documents have been verified and all questions have been resolved.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any substantial modification (i.e. any modification likely to have a significant impact on patient's protection, on the conditions of validity and on the results of the study, on the quality and security of data management, on the interpretation of scientific documents supporting the conduct of the study or on the methods of conducting it) will be the subject of a written amendment, submitted to the relevant authorities. A favourable opinion from the Comité de Protection des Personnes (CPP) is mandatory before the implementation of the amendment. All amendments to the protocol must be brought to the attention of all investigating surgeons participating in the study, who will respect their content. Any amendment that modifies the care of participants or the benefits, risks and constraints of the study, is subject to a new information note and a new consent form, the collection of which follows the same procedure as the one mentioned above.

Dissemination plans {31a}

At the end of the study, a patient has the right to be informed of the study results, according to the terms specified in the information note. All the data collected during this study are the property of the trial sponsor and cannot be communicated in any case to a third party without the written agreement of the sponsor. The study results will be submitted to peer-reviewed journals and presented at national and/or international conferences.

Discussion

The REMEDY trial is, to our knowledge, one of the only two studies evaluating limited fasciectomy with autologous adipose tissue grafting for Dupuytren's contracture. Sambuy et al. [23] reported more complications and worse functional results for limited fasciectomy with autologous adipose tissue grafting compared to limited fasciectomy alone. These results are surprising since the autologous adipose tissue grafting is already well described in the literature and has typically low risk of complications [11, 31]. Since the adipose tissue graft is autologous, harvested and implanted in a closed circuit without denaturation or adjuvant products, the risk of an immune response is close to none. In our prior clinical safety study of limited fasciectomy with autologous adipose tissue grafting, we have not observed an increase in complication rate in comparison to limited fasciectomy alone. As for the functional results evaluated by Sambuy et al. [23], the difference at 1-year follow-up using the brief Michigan Hand Outcomes Questionnaire (bMHQ) was of 3.78 (91.28 in the control group, 87.50 in the fat group). The difference was statistically significant; however, it could leave doubts on the clinical relevance as the difference was smaller than minimal clinically important difference for the bMHQ (10.4 points) [32]. The study by Sambuy et al. [23] was limited by a short follow-up and small sample size. We are planning to address these limitations in REMEDY trial by increasing the sample size and ensuring the follow-up of 5 years.

Trial status

Protocol version number and date: 2020-A03214-35, version 3.0 from 9 December 2021.

Recruitment start date: 13 June 2022.

Estimated recruitment end date: 01 June 2025.

Abbreviations

ADCs	Adipose-derived stem cells
AE	Adverse effect
CI	Confidence interval
CCH	Clostridium collagenase injection
CPP	Comité de Protection des Personnes (research ethics committee)
CRA	Clinical Research Associate
eCRF	Electronic case report form
GDPR	General Data Protection and Regulation
GEE	Generalised estimating equations model
LF	Limited fasciectomy
PALF	Percutaneous aponeurotomy and lipofilling
PHC	Public Health Code (Code de la Santé Publique)
PNF	Percutaneous needle fasciotomy
POSAS	Patient and Observer Scar Assessment Scale
QuickDASH	Quick Disabilities of the Arm, Shoulder and Hand
RCT	Randomised controlled trial
SAE	Serious adverse event
UAE	Unexpected adverse event

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Availability of data and materials {29}
The sponsor is responsible for obtaining the agreement of all the parties involved in the research in order to guarantee direct access to all the places where the research is carried out, to the source data, to the source documents and to the reports for quality control and audit. The investigating surgeons will make available the documents and individual data strictly necessary for follow-up, quality control and audit, to anyone who has the right to access these data in accordance with the current legislation (articles L.1121–3 and R.5121–13 of the PHC).

Declarations

Ethics approval and consent to participate {24}
The sponsor and the investigating surgeons agree that this research will be carried out in accordance with Law No. 2004–806 of August 9, 2004, as well as in accordance with Good Clinical Practices (I.C.H. version 4 of May 1, 1996, and decision of November 24, 2006) and the Declaration of Helsinki. The research is conducted in accordance with this protocol, except in emergency situations requiring the implementation of specific therapeutic acts. The investigating surgeons will respect all aspects of the protocol, in particular with regard to the collection of consent and notification and follow-up of SAEs. The present study was approved by the committee "Sud-Ouest et Outre-Mer I" of the CPP (2020-A03214-35) on 15/03/2021.
The patient will be informed orally and in writing through the information note about the objective of the research, the progress and duration of the study, the benefits, potential risks and constraints of the study as well as about the opinion given by the CPP (art. L.1122–1 CSP). The information note is supplemented with the information necessary to comply with the regulations on the protection of personal data (GDPR). The investigating surgeon must specify to the patient that they are totally free to accept or refuse their participation in the research and that they retain the right to withdraw from the study at any time for any reason without causing any prejudice, in particular professional one. The patient's participation in the protocol will be mentioned in their medical file at the time of the inclusion visit. All patients will provide written informed consent signifying their agreement to participate in the research before any study-specific assessment or procedure is performed (Art.L1122-1–1 CSP). No compensation is provided for the participation in this study.

Consent for publication {32}
Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on reasonable request.

Competing interests {28}
Thiebaud Biomedical Devices provided complimentary St'rim™ adipose tissue grafting system. The authors declare that they have no competing interests.

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