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Efficacy of the Gelstix nucleus augmentation device for the treatment of chronic discogenic low back pain: protocol for a randomised, sham-controlled, double-blind, multicentre trial

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ABSTRACT

Introduction Discogenic pain is the cause of pain in 26%–40% of patients with for low back pain. Consensus about treatment of chronic discogenic low back pain is lacking and most treatment alternatives are supported by limited evidence. The percutaneous implantation of hydrogels into the nucleus pulposus represents a promising regenerative intradiscal therapy. The hydrogel 'GelStix' is composed primarily of hydrolyzed polyacrylonitrile and acts as a reservoir of hydration, producing increased pressure and improved pH balance, potentially leading to disc preservation. We hypothesise that treatment with GelStix will lead to greater reduction in pain intensity at 6 months post-treatment compared with patients receiving sham treatment.

Methods and analysis This is a parallel group, randomised sham-controlled double-blind, multicentre trial to assess whether the GelStix device is superior to sham in reducing pain intensity in patients with chronic discogenic low back pain. The study will be conducted in two regional hospitals in Europe. Seventy-two participants will be randomised in a 1:1 ratio. The primary outcome will be the change in pain intensity between preoperative baseline and at 6 months postintervention. Secondary outcomes were disability, quality of life, the patient's global impression of change scale, the use of pain medication and the disc degeneration process assessed by means of MRI. For change in pain intensity, disability, health-related quality of life and disc height, mean values will be compared between groups using linear regression analysis, adjusted for treatment centre.

Ethics and dissemination Ethics approval was obtained from the Ethics Committee of the Canton Ticino, Switzerland (CE2982) and by the Medical Ethical Committee Arnhem-Nijmegen, the Netherlands (2016-2944). All patients that agree to participate will be asked to sign an informed consent form. Results will be disseminated through international publications in peer-reviewed journals, in addition to international conference presentations.

Strengths and limitations of this study

- This will be the first prospective, randomised, controlled, multicentre trial assessing effectivity and safety of the GelStix Nucleus Augmentation Device compared with a sham control in patients with lumbar discogenic pain that had no benefit from conservative care.
- Means to reduce risk of bias are implemented, which includes an a priori sample size calculation, an explicitly stated primary hypothesis to be tested, methodological rigour, double-blinding, randomisation, adequate concealment of group allocation and the assessment of the success of blinding in participants and observers.
- This is also the first study that assesses the disc degeneration process and disc height by means of MRI 1 year after GelStix implantation versus sham.
- All participants will also be treated according to a protocolised physiotherapy.
- A limitation of this trial is the uncertainty whether intradiscal saline injection is a true placebo, as it may have active effects.
- Other limitations of this study are those inherent to a prospective, randomised sham-controlled double-blind study, including strict exclusion criteria and thus limited generalisability (eg, protrusions in contact with any nerve root at the symptomatic level or >5 mm, an insufficient number of patients, and adherence to a strict protocol that does not necessarily reflect real-word daily practice).

Trial registration number NCT02763956.
Protocol version 7.1, 18 November 2020.

INTRODUCTION

Background and rationale

Discogenic low back pain is characterised by persistent, predominantly centralised

axial low back pain that worsens with axial loading. It is associated with intervertebral disc degeneration without herniation,[1–4] and is thought to be the cause of pain in 26%–40% of patients consulting a physician for low back pain.[5–9] The water-binding capabilities of the intervertebral disc diminish with aging[10] leading to progressive shrinking of the nucleus pulposus and loss of elasticity.[10–13] The cartilaginous endplate vascular flow decreases due to a progressive loss in vascularisation leading to accumulation of cellular waste products, and an increasingly acidic environment.[10 14] A low pH around the discus is associated with discogenic pain.[15 16]

Medical history, physical examination, and imaging (eg, MRI) provide inadequate sensitivity and specificity to accurately diagnose discogenic pain.[17–21] Despite an ongoing debate, moderate evidence supports diagnostic accuracy of provocative discography.[19 22 23] While previous studies suggest that high-pressure provocative discography may accelerate disc degeneration,[24–26] a recently published study suggests that low-pressure provocative discography, performed according to International Association for the Study of Pain (IASP) criteria, does not accelerate disc degeneration.[27]

Consensus about treatment of chronic discogenic low back pain is lacking and the majority of treatment alternatives is supported by limited evidence.[1 4] Conservative management includes anti-inflammatory drugs, physiotherapy and multidisciplinary biopsychosocial rehabilitation.[28] If conservative treatment fails, (minimally) invasive treatments are considered.[1] Most minimally invasive treatments, such as intradiscal injections (eg, with methylene blue) and thermal intradiscal/annular techniques (intradiscal electrothermal therapy, have been abandoned because of poor evidence.[29–31] A recent systematic review concluded that most minimal invasive treatments for discogenic low back have very low evidence; only biacuplasty has moderate evidence for a subgroup of patients with discogenic low back pain.[32]

Fusion surgery and total disc replacement, although contemplated as possible therapies in some cases, are invasive interventions associated with risk of adjacent segment disorder and morbidity.[4 33] In addition, fusion surgery is not superior to conservative treatment with multidisciplinary biopsychosocial rehabilitation and physiotherapy.[34 35] Recently, with the emergence of new frequencies (burst, dorsal root ganglion stimulation, high frequency-10 Hz), low back pain has become a good treatment option for neuromodulation. Considering the fact that neuromodulation is a more invasive treatment the need is great to find evidence for minimal invasive treatment for chronic discogenic low back pain.[36 37]

Therefore, treatment options filling the gap between conservative care and invasive surgical intervention are urgently needed. Currently the first studies are published showing effect of the use of platelet-rich plasma and mesenchymal signalling cells (MSCs) for discogenic pain. Notably, no intervention has multiple randomised controlled trials (RCTs) published yet.[38]

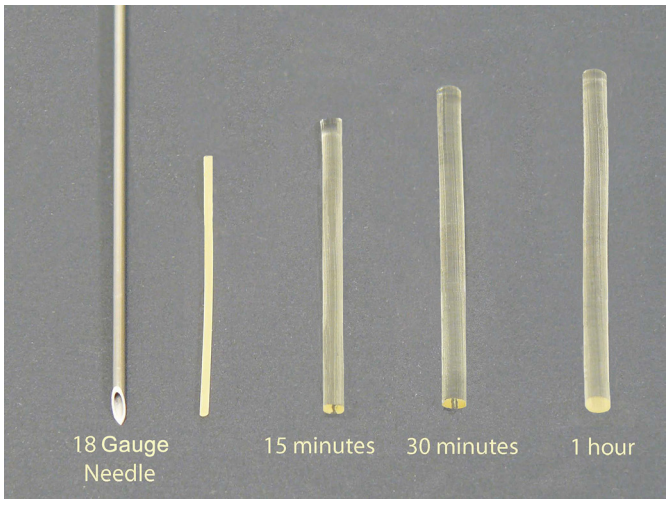

Figure 1 1835S GelStix. From left to right: 18 Gauge Needle, GelStix: dry, after 15 min hydration, after 30 min hydration, after 45 min hydration.

The implantation of hydrogels into the nucleus pulposus represents a promising regenerative intradiscal therapy, in particular in patients with early or moderate disc degeneration not responding to conservative care.[39 40] The hydrogel containing 'GelStix Nucleus Augmentation Device' (hereafter called GelStix) is composed primarily of hydrolyzed polyacrylonitrile. The GelStix is shaped in the form of an elongated matchstick and can be inserted percutaneously into the nucleus through a needle. Once implanted, the GelStix absorbs the body's own fluids and expands around tenfold in volume (see figure 1).

The GelStix material acts as a reservoir of permanent hydration of the intervertebral disc, producing increased pressure and improved fluid exchange and pH balance, leading to disc preservation.[41] Results of previous non-controlled studies suggest that GelStix implantation leads to a significant pain and disability relief 4 weeks after implantation in patients with discogenic pain.[42 43]

Objectives

The purpose of this study is to evaluate the efficacy and safety of GelStix compared with sham control in patients with chronic discogenic low back pain that had no benefit from conservative care. The primary outcome will be the change in pain intensity between preoperative baseline and at 6 months postintervention. Secondary outcomes include disability, quality of life (QOL) outcome measures, the patient's global impression of change (PGIC) scale, the use of pain medication and the disc degeneration process assessed by means of MRI.

We hypothesise that treatment with GelStix will lead to greater reduction in pain intensity at 6 months post-treatment compared with patients receiving sham treatment.

Trial design

This is a parallel-group, randomised sham-controlled double-blind, multicentre trial to assess whether the

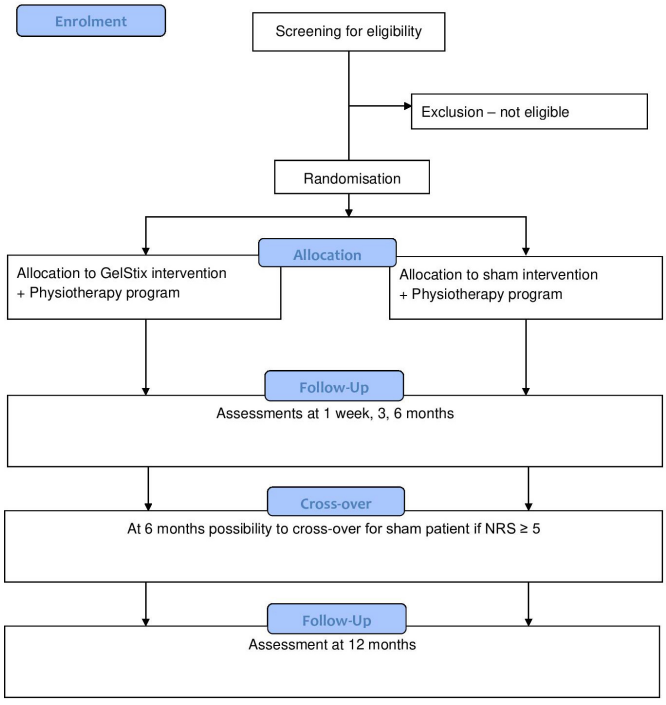

Figure 2 Study flow chart. NRS, Numeric Rating Scale.

GelStix device is superior to sham in reducing pain intensity in patients with chronic discogenic low back pain. Patients are randomly allocated in a 1:1 ratio. Figure 2 provides a flow diagram of the progress through the enrolment, intervention allocation, follow-up and data analysis phases of the trial.

METHODS AND ANALYSIS

This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials checklist. The study will be conducted in two regional hospitals in Europe: the Pain Management Centre, Neurocentre of Southern Switzerland, Lugano, Switzerland and the Department of Anaesthesiology and Pain Management Arnhem, Rijnstate Hospital, Arnhem, the Netherlands. Recruitment started in April 2016 and we included 42 participants till now. We expect to complete the study in 2025.

Participants

The target population is represented by patients suffering from discogenic low back pain with a baseline Numeric Rating Scale (NRS) pain score ≥5/10 following at least twelve weeks conservative care.

Inclusion criteria

- 18–66 years of age.
- Lumbar DDD on MRI scan with Pfirrmann grade[44] 2, 3 or 4.
- Discogenic pain confirmed by positive discography* of one or maximum two lumbar disc levels, and one negative control level.
- Persistent predominant, nociceptive low back pain with an NRS score of ≥5/10, that worsens with axial loading and improves with recumbence of at least 12 weeks duration.
- Failure to have symptoms resolved or reduced following at least 12 weeks conservative care (drug therapy and/or physiotherapy).
- Negative medial branches block results.
- Legally competent and able to understand the nature, scope and aim of the clinical investigation.

Exclusion criteria

- Radiculopathy caused by nerve root compression.
- Frank herniations, extruded or sequestered fragments, bulge/protrusions in contact with any nerve root at the symptomatic level or >5 mm in anteroposterior dimension.
- Greater than grade four annular tear (Adams scale).[45]
- Disc height less than 3 mm at the symptomatic level.
- Severe symptomatic central, foraminal or lateral recess stenosis, spondylolysis, spondylolisthesis greater than I out of IV, acute fractures, or ankylosing spondylitis at any lumbar disc level
- Coagulopathy or oral anticoagulant therapy (except low-dose acetylsalicylic acid) in conditions that do not allow for a temporary discontinuation.
- Active infection, systemically or localised.
- Any disease process or condition that may make the effect of the treatment difficult to evaluate (eg, cancer, substance abuse).
- Previous surgery at any lumbar disc level.
- Body mass index of ≥35 kg/m$^{2.}$
- Females of childbearing age that are known to be pregnant or wishing to be pregnant during the study.
- Psychological disorders or factors that may impact on treatment outcomes or compliance (eg, severe depressions).
- Participation in any other interventional study at the same time.

*Procedure of provocative discography.

Provocative discography will be performed by an experienced pain physician under strict sterile conditions. Thirty minutes before the intervention, intravenous antibiotics for prophylaxis will be administered. The patient will be positioned in the prone position on an X-ray permeable table. After subcutaneous anaesthetic injection of 2 mL mg of lidocaine 1%, the nucleus will be accessed with the two-needle technique with a 25–27 Gauge needle through the transforaminal, posterolateral approach, according to the technique described by Kallewaard *et al*.[3] Fluoroscopy will be used to identify spinal levels, guide the needle, and to confirm final needle position. The following variables will be monitored during the injection of the contrast solution: the opening pressure (the pressure at which contrast is first visible in the disc), the provocation pressure (the pressure greater than the opening pressure at which complaints of pain arise), and the peak pressure or the final pressure at the end of the

procedure. Additionally, the total volume of the injected contrast solution, the Adams scale,[45] and the pain score measured by NRS per disc level will be recorded.

The procedure, per level, is continued until:[3]

- Concordant pain is reproduced at a level of ≥7/10.
- The volume infused reaches 3.0 mL.
- The pressure rises to 50 psi above opening pressure.

According to the guidelines of the IASP,[46] the symptomatic level and the one adjacent level are examined. A disc is only considered to be positive if concordant pain can be induced at the target level (symptomatic level); with an intensity of this pain of at least NRS 7, reproduced by a pressure of less than 50 psi above opening pressure; and if the control level is negative for provocation of pain. A control disc is considered a critical element for defining a positive discography, as it serves as an internal patient control disc and as a possible indicator of central sensitisation.

Interventions

The GelStix implantation

For each participant, up to two levels will be treated. The CE marked GelStix Nucleus Augmentation Device system (STX-1835S, Replication Medical—Cranbury, New Jersey, USA), will be implanted by an experienced pain physician familiar with the transforaminal posterolateral discography approach described above. The GelStix insertion will be performed under local anaesthesia with a single needle technique through the procedure-specific 18 Gauge needle (18GTXX165mm, Replication Medical—Cranbury, New Jersey, USA). Up to three GelStixs will be implanted at each symptomatic disc level. Once the needle tip is located in the centre of the nucleus, the stylet will be removed from the needle. Then, the protective cap is removed from the preloaded GelStix holder and the GelStix holder is threaded onto the proximal end of the introducer needle. The holder stylet is pushed, driving the GelStix completely into the introducer needle. The implant holder will then be removed and the needle stylet ('blunt push rod needle') is driven through the needle and bottomed out to deliver the GelStix completely into the nucleus, keeping the needle tip centred in the nucleus (figure 3A–3F). The procedure will be repeated to insert additional GelStix. When resistance rises adding a second or third GelStix, further insertion is discontinued. At the end of the procedure, the needle will be withdrawn, and a sterile bandage will be applied to the insertion site.

The sham intervention

For the sham intervention the symptomatic discs will be injected with 1 mL of saline (NaCl 0.9%). Intradiscal saline injection (1 mL NaCl 0.9%) is safe[47] and has been used as a control/sham intervention in other randomised controlled.[29 48 49]

Concomitant treatment

Starting 2 weeks after the intervention, participants of both study groups will be prescribed physiotherapy

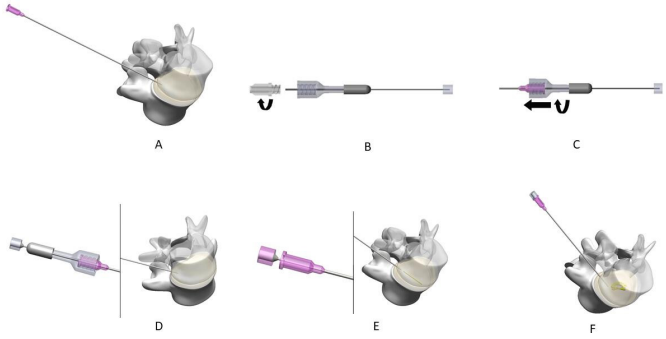

Figure 3 (A) Using fluoroscopic guidance, the needle is introduce using a standard posterolateral discography approach. (B) The protective cap is removed from the preloaded implant holder. (C) The implant holder is threaded onto the proximal end of the introducer needle. (D) The holder stylet is pushed so that the implant is driven completely into the introducer needle. (E) The implant holder is removed. The needle stylet is driven through the needle and bottomed out to deliver the GelStix completely into the nucleus, keeping the needle tip centred in the nucleus. (F) The needle tip will keep centred approximately in the nucleus and the procedure will be repeated to insert additional GelStix.

according to a study specific protocol. Session frequency will be once a week, for 9 weeks. An experienced musculoskeletal physiotherapist will assess the patient before starting the postintervention protocol, in order to determine the starting level for the exercises. Motor control and stabilisation exercises will be instructed to the patients and they will get a leaflet with pictures of the exercises to perform at home/at work. Individual exercises include training of the deep abdominal muscles with the lumbar multifidus and the transversus abdominis. Moreover, to restore the function of the core muscles, all directions and their muscular chains will be trained. All patients will be instructed as to how to do exercises at home and will be asked to continue these exercises three times a week for 6 months. Continuation or modification of pain medication is permitted during the study period of twelve months.

Outcome measures

The primary outcome is the change in pain intensity, assessed by means of a pain diary, between preoperative baseline and at 6 months postintervention in the GelStix-treated compared with the sham-treated group. Pain intensity will be assessed employing an 11-point (ie, 0–10) NRS with 0 meaning 'no pain' and '10' meaning 'worst possible pain'.[50] Three times daily pain scores will be assessed for five consecutive days around the intended measurement time. The mean NRS scores on the pain diary will furthermore be measured at 1 week, and 1, 3 and 12 months.

The secondary outcomes include:

- Disability, using the Oswestry Disability Index (ODI). The ODI is completed at baseline, and at three, six and twelve months. The ODI is a self-administered questionnaire, assessing the patient's level of pain and

function during basic activities of daily living such as walking, personal care, standing, sleeping, etc.[51]

- QoL, quantified with the European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L). The EQ-5D-5L will be completed at baseline and at three, six and twelve months. This questionnaire assesses health related QoL in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[52] Additionally, the EQ Visual Analogue Scale (EQ VAS) records the respondent's self-rated health on a 20 cm vertical, VAS with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'.
- The PGIC scale will be measured at three, six and twelve months. This scale assesses the patient's own evaluation of improvement or deterioration over time on a 7-point Likert Scale rated from 'very much improved' to 'very much worse'.
- The use of pain medication will be assessed as the intake of analgesics at baseline, at 1 week, and at 1, 3, 6 and 12 months.
- The disc degeneration process will be assessed by means of MRI twelve months after treatment compared with baseline. Pfirrmann grade,[44] disc height and the presence of high intensity zones (HIZ),[53] Modic signs[54] and Schmorl's nodes[55] will be recorded.

Additionally, to assess the association between pain catastrophising, surgical fear, state of depression and long-term outcome the following additional patient-reported outcome measures will be registered at baseline. Pain catastrophising, defined as an exaggerated negative interpretation of the meaning of pain, will be measured by the Pain Catastrophising Scale (PCS). Higher pain catastrophising before intervention are related to lower perceived recovery.[56 57] Surgical fear will be measured by the Surgical Fear Questionnaire (SFQ) as a predictor of physical and emotional recovery.[56] State of depression will be assessed by the Hospital Anxiety and Depression Scale (HADS), a self-administered questionnaire developed to detect states of anxiety and depression in hospital out-patient clinics.[58] Moreover, pain self-efficacy will be assessed employing the Pain Self-Efficacy Questionnaire-I (PSEQ-I). This patient self-reported measurement instrument evaluates pain self-efficacy beliefs,[59] that is, the degree of confidence a patient has in performing regular daily activities despite of pain. The presence of low levels of pain self-efficacy has been shown to be associated with high levels of disability in patients experiencing pain.[60 61]

The following additional data will be collected at baseline: sex, age, weight, height, smoking habits, previous treatment of discogenic pain and neurological examination. Employment status baseline and at 6 and 12 months will be recorded. The proportion of patients unable to return to work will be an additional measure of efficacy of the treatment.

The success of blinding will be assessed at the end of the trial. Before unblinding, the patients and the blind observers will be asked to guess the patients' treatment and the answers will be compared with the actual treatments administered. Successful blinding procedures can reduce bias in clinical trials.[62 63]

The safety outcome of this study is the incidence and severity of complications and adverse events (AE's) including procedure-related complications at any time point in the study. The main expected adverse device effects are infection (local or discitis), bleeding, nerve damage and/or limited motion as a result of the procedure.

Sample size

Twenty-eight patients per group will be required to have 80% power to detect a minimally clinically relevant difference of 1.5 points on the NRS between groups, with an estimated SD of 2, based on the pooled SD of NRS scores of similar patients in the RCT of Kallewaard *et al*,[29] and testing with an alpha of 5% (two tailed). With an expected drop-out rate of about 20%, a total of 72 patients will be randomised.

Randomisation

The Project Manager of the Clinical Trial Unit of the Ente Ospedaliero Cantonale, Bellinzona, Switzerland, will be in charge for computer generated block randomisation lists stratified by centre (blocks of 4). The project manager will act as an independent person, not involved in any other aspect of the trial except administrative/financial issues. The study is patient-blinded and observer-blinded, while the physician performing the study intervention will necessarily be aware of the treatment allocation. A web-based access to patient allocation codes will be provided to the physician in charge for GelStix/placebo injection. The treating team will be instructed not to communicate allocation to GelStix or placebo in any way, both to the patient and to other trial personnel. The 'assessors', that is, the investigators in charge for efficacy and safety assessments and the research nurses that may be in charge for questionnaires collection, and the personnel in charge of monitoring/data review and analysis will have no access to the randomisation lists and will receive no information about patient treatment for the entire duration of the study. For patients still experiencing substantial discogenic pain at 6 months, the code can be broken at their request (after the assessment of the success of blinding). The patients initially allocated to the control group are then given the opportunity to cross-over to the GelStix treatment. Any other code breaks should occur only in circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient, for example, in case of important AE's to ensure the most appropriate patient management.

Data collection and management

Study data will be collected on a case report form by the research team and will be entered in a Research Electronic Data Capture (REDCap) database.[64] The data will be associated to a unique trial identification number

per patient. The database will be double-checked for missing data and data entry errors. The data from the REDCap database will be imported automatically in the latest version of R, a language for statistical computing. All study data will be archived for at least 15 years after study termination.

Statistical methods

Baseline characteristics will be described stratified by treatment allocation as mean and SD or median and first and third quartile, and as count and percentage, as appropriate. In case of over 5% of missing data, we will use multiple imputation with fully conditional specification to impute the dataset. The number of imputations will be set to the percentage of incomplete patients. All subsequent analyses will be performed according to the intention to treat principle. A 'per-protocol' analysis will also be performed, excluding patients who are not evaluable for the primary endpoint because of drop-out (eg, consent withdrawal before completion of the 6 months observation period). Frequency and type of AE's and complications during the study will be described in the final report. Drop-outs will be replaced up to the number of evaluable patients defined in the sample size calculation.

The primary outcome is change in pain (NRS) at 6 months compared with baseline. Mean values will be compared between groups using linear regression analysis, adjusted for treatment centre. In case of imbalance of baseline characteristics as judged by the trial steering committee, regression analyses will be further adjusted for potential confounders. This adjustment will be performed as stratified randomisation induces correlated observations, which should be accounted for. By adjusting for treatment centre, the analyses yield correct p values and confidence intervals with the correct coverage, and results in more power compared with unadjusted analyses.[65]

Change from baseline in pain at other follow-up moments and change from baseline in continuous secondary outcome measures (ie, disability (ODI) and health related QoL (EQ-5D-5L), and disc height) will be analysed in a similar manner. PGIC scores will be dichotomised by taking 'very much improved' and 'much improved' to indicate treatment success. Pfirrmann grade will be dichotomised into grade 1 or 2 vs more than 2. Success rates on the PGIC, dichotomised Pfirrmann grade and the presence of HIZ, Modic changes, and Schmorl's nodes will be compared between groups using logistic regression analysis adjusted for centre.

Univariable and multivariable logistic regression will be used to quantify crude and adjusted associations between PCS, SFQ, HADS and PSEQ-I and treatment success. These analyses will be considered exploratory. The success of blinding will be assessed using the Sign test, testing whether the percentage of correct guesses differs from that expected by chance (ie, 50%).

Monitoring

The research project will be monitored by a certified clinical monitor, which will review the data quality and will ensure that study activities are carried out in accordance with the protocol, good clinical practice and applicable regulatory requirements. This being a novel treatment method, a blinded interim analysis for futility will be planned for the primary outcome measure at T3 months after 40 patients (ie, 20 in each arm of the study) have been enrolled. The study will be terminated in case the experimental arm performs significantly worse (as based on independent samples t-test or Mann-Whitney U test) and the difference between groups is clinically relevant (ie, 2 points or more on the NRS).

Limitations of the study

The limitations are those inherent to a prospective, randomised, sham-controlled study, including difficulty in recruiting patients due to potential patient refusal and strict exclusion criteria (eg, protrusions in contact with any nerve root on the symptomatic level or >5 mm), an insufficient number of patients and adherence to a strict protocol that does not necessarily reflect real world daily practice. Recently performed strategies for achieving adequate participant enrolment to reach target sample size are the drafting and dispersal of an informative letter to referral colleagues in Switzerland and in the Netherlands, the introduction of a back pain treatment algorithm in the Pain Management Centre in Lugano, indicating a clear algorithm to follow after negative medial branch block tests, indicating also the possibility for inclusion in the GelStix study.

Another limitation of this trial is the question whether intradiscal saline injection is a true placebo, as it may have active effects. For example, a recently published systematic review and meta-analysis of Manchikanti *et al* showed that epidurally administered saline and saline with steroids may be both effective in managing low back and lower extremity pain.[66] On the other hand, saline has been routinely used as a sham intervention in several other intradiscal treatment studies such as the RCT of Kallewaard *et al*,[29] which compared intradiscal methylene blue plus lidocaine to intradiscal saline plus lidocaine injection, and two the RCTs of Cao *et al*[48] and Khot *et al*[49] comparing intradiscal corticosteroid to saline injection in the treatment of discogenic low back pain. To reduce the risk of a bias due to the uncertainty saline injection being a true placebo, a third 'no treatment group' (receiving only physiotherapy treatment) could be added to this study. However, we regard adding a third 'no treatment group' to this study not feasible, mainly because of the expected difficulties in patient recruitment.

Patient and public involvement

Patient with discogenic pain were involved at several stages of the trial, including the design and conduct of the trial. We carefully assessed the burden of the trial interventions on these patients. We will disseminate the

main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

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Contributors EK, PM, J-WK, LS, AC and SMJvK designed the study. EK, PM, J-WK, JD, LS, AC, PS, DEK will conduct the study including patient recruitment and data collection. SMJvK will conduct the data analysis and will conduct the interpretation of the data. EK drafted the manuscript with important intellectual input from J-WK, PM, SMJvK, AC, JD, MWH, LS, PS and DEK. All authors approved the final manuscript. EK, J-WK, PM and JD will have complete access to the study data.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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