

**A prospective, randomized, controlled, single centre trial to assess the efficacy and safety of radial extracorporeal shock wave therapy in patients with chronic non-specific low back pain**

<b>INVESTIGATORS</b>	<b>ROLE</b>
Prof. (Ms.) Ziyiing FENG, MD Department of Pain Medicine First Affiliated Hospital of Zhejiang University 79 Qingchun Road Hangzhou Zhejiang Province China, 310003 E-mail: 13989881666@163.com	Principal Investigator
Prof. Dr. Christoph Schmitz, MD Extracorporeal Shock Wave Research Unit Department of Anatomy II Ludwig-Maximilians-University 11 Pettenkoferstr. Munich, 80336 Germany Phone: +49-89-2180-72620 Fax: +49-89-2180-72683 E-mail: christoph_schmitz@med.uni-muenchen.de	Co-Author

# 1. Background

Non-specific low back pain is defined as low back pain not attributable to a recognizable, known specific pathology (e.g., infection, tumour, osteoporosis, fracture, structural deformity, inflammatory disorder, radicular syndrome, or cauda equina syndrome) (Balagué et al., 2012). Non-specific low back pain is common and affects people of all ages (e.g., Carragee, 2005; Bhangle et al., 2009; Maher et al., 2017). It is second only to the common cold as the most common affliction of mankind and is among the leading complaints bringing patients to physicians' offices (e.g., Bhangle et al., 2009; Maher et al., 2017). The reported point prevalence of non-specific low back pain is as high as 33 percent (e.g., Skovron et al., 1994; Maher et al., 2017), its one-year prevalence as high as 73 percent (e.g., Cassidy et al., 1998; Maher et al., 2017) and its lifetime prevalence exceeds 70% in most industrialized countries (Balagué et al., 2012), with an annual incidence of 15% to 20% in the United States of America (Bhangle et al., 2009). In physically active adults not seeking medical attention, the annual incidence of clinically significant non-specific low back pain (pain level, 4 or more on a 10-point scale) with functional impairment is approximately 10 to 15 percent (Carragee et al., 2005). In China, non-specific low back pain has become one of the leading causes of disability-adjusted life-years (DALYs) in 2010, next to cardiovascular diseases (stroke and ischaemic heart disease), cancers (lung and liver cancer) and depression (Yang et al., 2013). Zhang et al. (2015) reported the prevalence of non-specific low back pain as 41% in Chinese adolescents, and a close relationship between non-specific low back pain and self-reported academic pressure.

An alarming increase in the prevalence of chronic non-specific low back pain has been observed in industrialized countries over the last years. For instance, in North Carolina (USA) the prevalence of chronic, impairing non-specific low back pain increased from 3.9 percent in 1992 to 10.2 percent in 2006 (Freburger et al., 2009). Increases were seen in both men and women, and across all ages and racial and ethnic groups. In China, the years lived with disability (YLDs) showed a 44% increase from 1990 to 2010 (Yang et al., 2013). (Note that different definitions of chronicity of non-specific low back pain were proposed in the literature, mainly characterized by the duration of symptoms (c.f. Cedraschi et al., 1999), e.g.: (i) more than seven weeks (Spitzer et al., 1987); (ii) more than three months (Nachemson and Bigos, 1984; Frymoyer, 1988; Frank, 1993); and (iii) at least half the days in a 12-month period in a single or in multiple episodes (Von Korff, 1994). In the proposed study chronicity will be defined as duration of symptoms of more than three months).

The social and economic impact of non-specific low back pain is substantial. It is the most frequent cause of disability for people under age 45. In 2005, the mean age- and sex-adjusted medical expenditure in the USA among respondents with spine problems was US\$ 6,096 vs US\$ 3,516 in those without spine problems, and it had increased by 65% (adjusted for inflation) from 1997 to 2005 (Martin et al., 2008).

Management for patients with non-specific low back pain is challenged by the problems that most back pain has no recognizable cause (>85%), an underlying systemic disease is rare, and most episodes of back pain are unpreventable (e.g., Carragee, 2005; Bhangle et al., 2009; Maher et al., 2017).

Acute non-specific low back pain (lasting three to six weeks) usually resolves in several weeks, although recurrences are common and low-grade symptoms are often present years after an initial episode. Risk factors for the development of disabling chronic or persistent non-specific low back pain (variously defined as lasting more than three months or more than six months) include preexisting psychological distress, disputed compensation issues, other types of chronic pain, and job dissatisfaction (Carragee et al., 2005; Hoy et al., 2010; Stubbs et al., 2016).

The goals of management for patients with non-specific low back pain are to (i) decrease the pain, (ii) restore mobility, (iii) hasten recovery so the patient can resume normal daily activities as soon as possible, (iv) prevent development of a chronic recurrent condition, and (v) restore and preserve physical and financial independence and comfort (Bhangle et al., 2009).

In February 2017 the American College of Physicians issued a novel guideline for treating nonradicular low back pain (Qaseem et al., 2017), as follows (quoted from Qaseem et al., 2017):

- Recommendation 1: given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select nonpharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants (moderate-quality evidence). (Grade: strong recommendation).
- Recommendation 2: for patients with chronic low back pain, clinicians and patients should initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction (moderate-quality evidence), tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level

laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation (low-quality evidence). (Grade: strong recommendation).

- Recommendation 3: in patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence).

Unfortunately, few if any treatments have been proven effective for non-specific low back pain in meta-analyses, including limited bed rest (Dahm et al., 2010), physical activity and exercise (Geneen et al., 2017), back schools (Poquet et al., 2016), traction (Wegner et al., 2013), massage (Furlan et al., 2015), chiropractic (Rubinstein et al., 2011; 2012), radiofrequency denervation (Mass et al., 2015), paracetamol (Saragiotto et al., 2016), opioids (Chaparro et al., 2013) and, ultimately, surgery (in cases of cauda equina syndrome, infections, tumors and fractures compressing the spinal cord, mechanical instability of the back, and, perhaps, intractable pain with a positive straight-leg-raising test and no response to conservative therapy) (Lawrence et al., 2008; Globe et al., 2008; Bhangle et al., 2009; Machado et al., 2009). Earlier studies demonstrated that muscle relaxants are effective in the management of non-specific low back pain, but the adverse effects require that they be used with caution (van Tulder et al., 2003). Accordingly, the aforementioned guideline by the American College of Physicians is only based on low- and moderate-quality evidence (see also Chou et al., 2016).

This highly unsatisfying situation is also reflected by the randomized controlled clinical trials on non-specific low back pain listed in the Physiotherapy Evidence Database (PEDro; <https://www.pedro.org.au/simplified-chinese/> or <https://www.pedro.org.au/traditional-chinese/>) (as of May 09, 2017). The PEDro database is a freely available database of over 36,000 randomized controlled trials (RCTs), systematic reviews and clinical practice guidelines in physical and rehabilitation medicine. For each RCT, review or guideline, the PEDro database provides the citation details, the abstract, and a link to the full text, where possible. All RCTs listed in the PEDro database are independently assessed for quality (the assessment criteria are summarized in Table 1). All but two of the PEDro scale items are based on the Delphi list (Verhagen et al., 1998). PEDro is currently the largest independent database on topics related to physical and rehabilitation medicine, and is often used by investigators in Norway, Australia, and New Zealand; less so by other European and North American investigators. Non-specific

low back pain was addressed in more than 1800 RCTs listed in the PEDro database. Table 2 summarized those RCTs listed in the PEDro database that received 10 or 9 points on the PEDro quality scale (as of May 09, 2017). It becomes obvious that these studies do not provide the basis for a conclusive recommendation how to treat non-specific low back pain.

**Table 1.** Assessment criteria of the PEDro database (modified from [www.pedro.org.au](http://www.pedro.org.au)).

<b>Part 1: criteria for inclusion of clinical trials in PEDro (all criteria must be fulfilled)</b>	
	<ul style="list-style-type: none"> <li>• The trial must involve comparison of at least two interventions. One of these interventions could be a no treatment control, or a sham treatment.</li> <li>• At least one of the interventions being evaluated must be currently part of physiotherapy practice or could become part of physiotherapy practice. However, the study need not be carried out by physiotherapists.</li> <li>• The interventions should be applied to subjects who are representative (or who are intended to be representative) of those to whom the intervention might be applied in the course of physiotherapy practice.</li> <li>• The trial should involve random allocation or intended-to-be-random allocation of subjects to interventions.</li> <li>• The paper must be a full paper (not an abstract) in a peer-reviewed journal.</li> </ul>
<b>Part 2: assessment criteria of clinical trials included in PEDro</b>	
<b>No.</b>	<b>Assessment criterion</b>
1*	Eligibility criteria were specified.
2	Subjects were randomly allocated to groups.
3	Allocation was concealed.
4	The groups were similar at baseline regarding the most important prognostic indicators.
5	There was blinding of all subjects.
6	There was blinding of all therapists who administered the therapy.
7	There was blinding of all assessors who measured at least one key outcome.
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”.
10	The results of between-group statistical comparisons are reported for at least one key outcome.
11	The study provides both point measures and measures of variability for at least one key outcome.

\* This criterion influences external validity, but not the internal or statistical validity of the trial. It has been included in the PEDro scale so that all items of the Delphi scale<sup>9</sup> are represented on the PEDro scale. This item is not used to calculate the PEDro score.

**Table 2.** All randomized controlled trials on non-specific low back pain listed in the PEDro database (www.pedro.org.au) (as of May 09, 2017) that received 10 or 9 points on the PEDro quality scale shown in Table 1.

P	Study	T	O	Main outcome
10	Glazov et al. (2014)	C	--	Infrared laser acupuncture not superior to placebo treatment
10	Konstantinovic et al. (2010)	A	+	Nimesulide 200 mg/day and low-level laser therapy superior to nimesulide 200 mg/day and placebo LLLT or nimesulide alone
9	Arguisuelas et al. (2016)	C	++	Myofascial Release protocol (MFR) superior to sham MFR
9	Corrêa et al. (2016)	C	--	Interferential current (IFC) not superior to placebo IFC
9	Panagopoulos et al. (2015)	*	-	Standard physiotherapy plus visceral manipulation not superior to standard physiotherapy alone
9	Hsieh et al. (2014)	C	-	Hotpack plus short-term 890-nm light therapy not superior to hotpack plus placebo light therapy
9	Parreira et al. (2014)	C	--	Kinesio taping with 10 to 15% tension applied in flexion to create skin convolutions in neutral not superior to kinesio taping without tension
9	Vas et al. (2014)	C	++	True auriculopressure superior to placebo auriculopressure
9	Licciardone et al. (2013a)	C	++	Osteopathic manual treatment (OMT) superior to sham OMT
9	Pach et al. (2013)	C	-	Individualized acupuncture not superior to standardized acupuncture
9	Licciardone et al. (2013b)	C	-	Osteopathic manual treatment not superior to ultrasound therapy
9	Sharpe et al. (2012)	A+C	++	Attention bias modification (ABM) superior to sham ABM
9	Castro-Sánchez et al. (2012)	C	--	Kinesio taping over the lumbar spine not superior to sham taping
9	Chen et al. (2012)	C	++	Functional fascial taping superior to placebo taping
9	Wang et al. (2012)	C	+	Core stability training superior to conventional exercise
9	Buchmuller et al. (2012)	C	--	TENS not superior to sham TENS
9	Costa et al. (2009)	C	--	Motor control exercise not superior to placebo (detuned ultrasound therapy and detuned short-wave therapy)
9	Glazov et al. (2009)	C	--	Infrared laser acupuncture not superior to placebo treatment
9	Koopman et al. (2009)	C	--	Microcurrent therapy not superior to placebo
9	Hancock et al. (2008)	A	-	Spinal manipulative therapy (SMT) plus paracetamol plus advice not superior to sham SMT plus paracetamol plus advice
9	Kennedy et al. (2008)	A	--	Acupuncture not superior to placebo
9	Hancock et al. (2007)	A	--	Diclofenac 50 mg twice daily (D) and spinal manipulative therapy (SMT) not superior to D plus placebo SMT, placebo D and SMT or double placebo
9	Pengel et al. (2007)	SA	++	Physiotherapist-directed exercise and advice superior to placebo
9	Brinkhaus et al. (2006)	C	++	Acupuncture superior to placebo
9	Santilli et al. (2006)	A	++	Active manipulations superior to simulated manipulations
9	Brizzi et al. (2004)	C	++	Hydrofor applications of a mixture containing both NSAIDs and muscle relaxants superior to Hydrofor applications of a drug-free solution
9	Kovacs et al. (2003)	C	+	Medium-firm mattresses superior to firm mattresses
9	Beurskens et al. (1997)	C	--	Traction not superior to placebo
9	Hadler et al. (1987)	A	+	Spinal manipulation superior to spinal mobilization without the rotational forces and leverage required to move facet joints.

P, points on the PEDro quality scale; T, type of study; A, acute non-specific low back pain; SA, subacute non-specific low back pain; C, chronic non-specific low back pain; \*, new episode of non-specific low back pain (defined as an episode which was preceded by a period of at least one month without non-specific low back pain); O, outcome; ++ investigated therapy statistically significantly ( $p < 0.05$ ) superior to placebo treatment; +, investigated therapy superior to alternative therapy ( $p < 0.05$ ); -, investigated therapy not superior to alternative therapy ( $p < 0.05$ ); --, investigated therapy not superior to placebo treatment ( $p < 0.05$ ).

Recently extracorporeal shock wave therapy (ESWT) was introduced into the management of non-specific low back pain (Nedelka et al., 2014; Lee et al., 2014; Han et al., 2015; Moon et al., 2016). The use of extracorporeal shock waves (ESWs) in medicine was first reported over 30 years ago as a treatment for kidney stones (Chaussy et al., 1980), and is commonly referred to as 'extracorporeal shock wave lithotripsy', or 'ESWL' (Rassweiler et al., 2011). Extracorporeal

shock waves are also used as a treatment for various musculoskeletal conditions such as calcifying tendinopathy of the shoulder, epicondylitis, Achilles tendinopathy and plantar fasciopathy (e.g., Speed, 2014; Schmitz et al., 2015), and is commonly referred to as 'extracorporeal shock wave therapy', or 'ESWT' to differentiate from ESWL (Speed, 2014). By means of a systematic review of data derived from the PEDro database Schmitz et al. (2015) demonstrated that ESWT is effective and safe, and for the aforementioned conditions RCTs on ESWT were the predominant type of RCT listed in the PEDro database and/or obtained the highest PEDro scores among all investigated treatment modalities.

There are three different types of ESWs used in ESWT for musculoskeletal conditions, focused, defocused and radial (Fig. 1 below), and several modes of operation of focused, defocused and radial extracorporeal shock wave generators (Fig. 2 below). Focused, defocused and radial ESWs are single acoustic impulses with an initial high positive peak pressure between 10 and 100 megapascals (MPa) reached in less than one microsecond ( $\mu$ s) (Rompe et al., 2007). The positive pressure amplitude is followed by a low tensile amplitude of a few microseconds duration that can generate cavitation (Chitnis and Cleveland, 2005; Schmitz et al., 2013; Angstman et al., 2015; Császár et al., 2015). They are further characterized by a short life cycle of approximately 10-20  $\mu$ s and a broad frequency spectrum. Focused ESWs differ from radial ESWs in the penetration depth into the tissue, some physical characteristics, and the technique for generating them (Ogden et al., 2001; Schmitz et al., 2013; Császár et al., 2015). However, without going into detail, there is no scientific evidence in favor of either radial ESWT (rESWT) or focused ESWT (fESWT) with respect to treatment outcome, and no scientific evidence that a certain fESWT technology is superior to the other technologies (Schmitz et al., 2015).

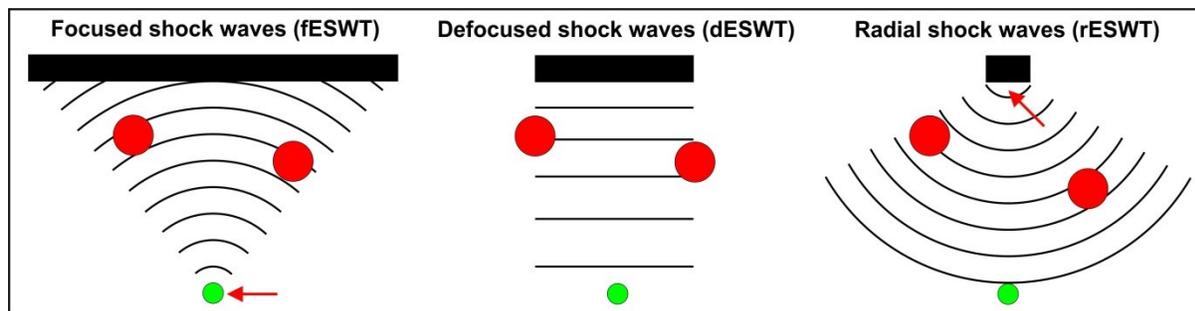
Several molecular and cellular mechanisms were reported on how ESWs might mediate their pain-relieving action. Specifically, exposure of the distal femur of rabbits to focused ESWs decreased the amount of Substance P (SP) in the periosteum (Maier et al., 2003) and diminished the number of neurons immunoreactive for substance P in dorsal root ganglia L5 (Hausdorf et al., 2008). Furthermore, application of shock waves to rat skin decreased calcitonin gene-related peptide (CGRP) immunoreactivity in dorsal root ganglion neurons (Takahashi et al., 2003). Substance P is concentrated in unmyelinated C-fibers (responsible for throbbing, chronic pain; Kandel et al., 2000) and a subpopulation of slowly conducting, lightly myelinated A- $\delta$  nerve fibers, and is released at central and peripheral terminals of sensory nociceptive neurons after stimulation (Keen et al., 1982; Malcangio and Bowery, 1999; Snijdelaar et al., 2000). CGRP is a marker of sensory neurons typically involved with pain perception and was

immunohistochemically co-localized with substance P in capsaicin-sensitive axons (Gibbins et al., 1985). Activation of peripheral small diameter sensory neurons by local depolarization, axonal reflexes, or dorsal root reflexes releases substance P and CGRP. Both substances then act on target cells in the periphery such as mast cells, immune cells and vascular smooth muscle cells, thus producing inflammation. This phenomenon is called neurogenic inflammation, and is an inflammatory symptom that results from the release of substances from primary sensory nerve terminals (Holzer, 1988; Richardson and Vasko, 2002). Evidence has emerged that chronic inflammation contributes to the etiology of pain in insertion tendinopathies such as tennis elbow and chronic plantar fasciitis (LeMelle et al., 1990; Schepsis et al., 1991; Roetert et al., 1995). Furthermore, Uchio et al. (2002) found that SP (as well as interleukin 1 alpha and transforming growth factor beta-1) are involved in the pathogenesis of tennis elbow, without apparent infiltration of inflammatory cells. Moreover, depletion of substance P was repeatedly shown to reduce experimentally induced inflammation of paws and joints in laboratory animals (Lam and Ferrell, 1991; Cruwys et al., 1995; Garrett et al., 1997). It is therefore reasonable to hypothesize that reduction of SP and CGRP in the target tissue (Maier et al., 2003; Takahashi et al., 2003) in conjunction with reduced synthesis of this molecule in dorsal root ganglia cells (Hausdorf et al., 2008) plays an important role in ESWT-mediated long-term analgesia in the treatment of musculoskeletal conditions.

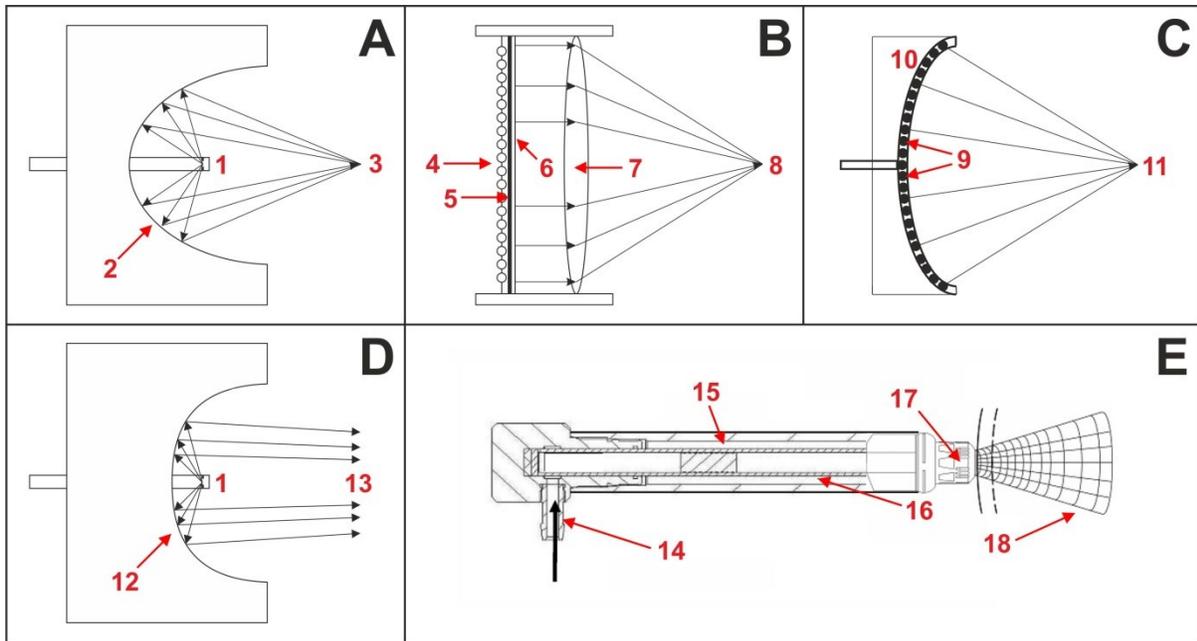
With respect to non-specific low back pain it is important to note that in rats, the presence of SP and CGRP immunoreactive nerve fibers was demonstrated in the lumbar facet joints (Ohtori et al., 2000). Furthermore, SP immunoreactive fibers were found more extensively in lumbar intervertebral discs from patients with discogenic low back pain than in normal control discs, together with the formation of a zone of vascularized granulation tissue from the nucleus pulposus to the outer part of the annulus fibrosus along the edges of the fissures (Peng et al., 2005). These findings suggested that the zone of granulation tissue with extensive innervation along the tears in the posterior part of the painful disc may be responsible for causing the pain of discography and of discogenic low back pain (Peng et al., 2005). Accordingly, ESWT could be of great significance in the treatment of persistent non-specific low back pain.

It is critical to note that the energy signature of ESWT devices fundamentally differs from the energy signature of certain “mechanical shockwave devices” utilized for spinal manipulative therapy (Liebscher et al., 2014). Furthermore, ESWT must not be confused with treatments that apply vibration at a low frequency (10, 50, 100, or 250 Hz), causing an oscillatory pressure (described as shock wave therapy by Seco et al., 2011). Seco et al’s (2011) statement that, strictly speaking, both shock waves and ultrasound could be referred to as “vibrotherapy”,

because both use vibration with a therapeutic goal, does not consider fundamental differences between the energy signature of ESWT devices and the energy signature of vibrating massage devices, as shown by Angstman et al. (2014).



**Fig. 1** (modified from Schmitz et al., 2015). Working principle of focused (on the left), defocused (in the middle) and radial (on the right) extracorporeal shock wave technology. In case of focused shock waves, single acoustic pulses are generated either with a spark-gap (electrohydraulic principle), a technology similar to a loudspeaker (electromagnetic principle), or piezocrystals (piezoelectric principle) (black bars represent shock wave generators; details are provided in Fig. 2). By means of reflectors of certain shape and/or the use of acoustic lenses the acoustic pulses are converted into a focused acoustic pressure wave/shock wave with a point of highest pressure (red arrow) at the desired target (green dot) within pathological tissue. By changing the shape of the reflector (and/or the acoustic lens) the acoustic waves emitted from a focused shock wave generator can be converted into a slightly convergent, parallel, or even divergent acoustic pressure wave/shock wave (“defocused shock wave”). In case of radial shock waves, a projectile is fired within a guiding tube that strikes a metal applicator placed on the skin. The projectile generates stress waves in the applicator that transmit pressure waves into tissue. The point of highest pressure is found at the tip of the applicator. It is of note that any disturbance in the pathway of the acoustic pulses between a focused shock wave source and the target within tissue (such as bone, calcifications, etc.; red dots in the figures) may result in some parts of the acoustic pulse not reaching the target and, thus, weakening the shock wave energy (i.e. the energy flux density) at the target. The same disturbances would not impact the energy of radial shock waves at the target (for defocused shock waves it is unknown to what extent they are weakened by disturbance in the pathway of the acoustic pulses between the shock wave source and the target within tissue). This is most probably the reason why in muscle tissue, the energy of focused shock waves was found to be decreased by >50% compared to measurements in water, whereas for radial shock waves measurements in muscle tissue and water were consistent (Kearney et al., 2010).



**Fig. 2** (modified from Schmitz et al., 2015). Schematic representation of the mode of operation of focused (A-C), defocused (D) and radial I extracorporeal shock wave generators. (A) Electrohydraulic principle (fESWT): a high voltage discharges rapidly across two electrode tips (spark-gap) (1) that are positioned in water. The spark-gap serves as the first focal point (1). The heat generated by this process vaporizes the surrounding water. This generates a gas bubble centered on the first focal point, with the gas bubble being filled with water vapor and plasma. The result of the very rapid expansion of this bubble is a sonic pulse, and the subsequent implosion of this bubble causes a reverse pulse, manifesting a shock wave. By means of reflectors of certain shape (2), this shock wave can be converted into a convergent/focused acoustic pressure wave/shock wave with a point of highest pressure at the second focal point (3). (B) Electromagnetic principle (fESWT): a strong, variable magnetic field is generated by passing a high electric current through a coil (4). This causes a high current in an opposed metal membrane (5), which causes an adjacent membrane (6) with surrounding liquid to be forced rapidly away. Because the adjacent membrane is highly conductive, it is forced away so rapidly that the compression of the surrounding liquid generates a shock wave within the liquid. By means of an acoustic lens (7) of certain shape, this shock wave can be converted into a convergent/focused acoustic pressure wave/shock wave with a point of highest pressure at a focal point (8). (C) Piezoelectric principle (fESWT): a large number of piezocrystals (9) are mounted in a bowl-shaped device (10); the number of piezocrystals can vary from a few to several thousands (typically between 1,000 and 2,000). When applying a rapid electrical discharge, the piezocrystals react with a deformation (contraction and expansion), which is known as the piezoelectric effect. This induces an acoustic pressure puls in the surrounding water that can steep into a shock wave. Because of the design of the bowl-shaped device an acoustic pressure wave/shock wave can

emerge with a point of highest pressure at a focal point (11). (D) Defocused principle (shown here for the electrohydraulic principle). By changing the shape of the reflector (12) the shock wave emitted from the first focal point is converted into a slightly convergent, parallel, or even divergent acoustic pressure wave/shock wave (“defocused shock wave”) (13). I Ballistic principle (rESWT): compressed air (pneumatic principle; 14) or a magnetic field (not shown) is used to fire a projectile (15) within a guiding tube (16) that strikes a metal applicator (17) placed on the patient’s skin. The projectile generates stress waves in the applicator that transmit pressure waves into tissue (18).

The studies on ESWT for non-specific low back pain performed so far (summarized in Table 3) have only established very limited evidence of efficacy and safety of ESWT for non-specific low back pain. This is due to low sample size, lack of power analyses, lack of reporting critical information such as the follow-up interval, and the fact that only one RCT on this indication was performed so far.

**Table 3.** Details of all studies on ESWT for non-specific low back pain listed in PubMed as of May 09, 2017.

Study	Nedelka et al. (2014)	Lee et al. (2014)	Han et al. (2015)	Moon et al. (2016)
Diagnosis	Unilateral chronic lumbar facet pain	Chronic low back pain	Chronic low back pain	Sacroiliac joint pain
Type of study	Pilot retrospective study	Cohort study (no randomization)	Cohort study (no randomization)	Randomized controlled trial
Power analysis	Not reported	Not reported	Not reported	Not reported
ESWT:				
No. of patients	21	13	15	15
Device	Duolith, radial part (Storz Medical, Tägerwillen, Switzerland)	JEST-2000 (Joeun Medical, Daejeon, Korea)	VITERA (Comed, Korea)	Unknown
Type of ESWT	Radial	Radial	Focused, electrohydraulic	
Applicator	15-mm titanium DPI applicator	17-mm head	17 mm head	
No. of ESWT sessions	5	12	12	1
Interval between ESWT sessions [days]	7	3.5 (two sessions per week)	3.5 (two sessions per week)	N/a
No. of shock waves per ESWT session	3000	2000	1000	2000
Bar / EFD of shock waves	3.5 / 0.12 mJ/mm <sup>2</sup>	0.10 mJ/mm <sup>2</sup>	0.01-0.16 mJ/mm <sup>2</sup>	Unknown
Frequency of shock waves [Hz]	Not provided	7	7	Unknown
Additional treatment	N/a	Exercise program	N/a	N/a
Alternative treatment 1				
No. of patients	20	15	15	15
Procedure	C: single injection of 6 ml 1% trimecaine and 7 mg of betamethazone	CPT: Conservative physical therapy, comprising hyperthermia using hot packs, ultrasound and TENS (details not provided)	CPT: Conservative physical therapy, comprising hyperthermia using hot packs (20 min), ultrasound (5 min) and TENS (15 min)	Sham ESWT
Alternative treatment 2		N/a	N/a	N/a
No. of patients	20			
Procedure	RMBN: Radiofrequency Medial Branch Neurotomy			
Follow-up interval	M2, M6 and M12	Not provided	Not provided	W1 and W4
Investigated variables	Pain (VAS score), Oswestry Disability Index	Pain (VAS score), dynamic balance ability	Pain (VAS score), Oswestry Disability Index, Beck depression index	Pain (VAS score), Oswestry Disability Index,
Definition of treatment success	Not provided	Not provided	Not provided	Not provided
VAS at baseline (ESWT)	Not provided	7.2 ± 0.8 (SD? SEM?)	7.0 ± 0.76 (SD? SEM?)	6.42 ± ?
VAS at follow-up (ESWT)	Not provided	4.5 ± 1.1 (SD? SEM?)	3.6 ± 1.1 (SD? SEM?)	3.64 ± ?
Outcome	RMBN > rESWT > C	ESWT > CPT	ESWT > CPT	ESWT > Sham ESWT

EFD, energy flux density; M, month, W, week.

Accordingly, further research is needed to support the use of ESWT for non-specific low back pain. Taking into account (i) the well-known molecular and cellular mechanisms of action of ESWT in pain relief (outlined in detail above), (ii) the proven efficacy and safety of rESWT for treating musculoskeletal conditions (Schmitz et al., 2015), and (iii) the fact that the rESWT

device Swiss DolorClast (Electro Medical Systems, Nyon, Switzerland) has become by far the best investigated ESWT technology in the field of Evidence Based Medicine (Table 4), it is reasonable to hypothesize that treatment of non-specific low back pain with the Swiss DolorClast is not only effective and safe but will get widespread acceptance and clinical use as soon as effectiveness and safety will be demonstrated in a randomized controlled trial. This is the purpose of the proposed project.

**Table 4.** Devices used in all studies on ESWT listed in the PEDro database as of January 01, 2017 (note that in some studies the name of the used device was not mentioned).

Device	T	Manufacturer	No. of studies
DolorClast	R	Electro Medical Systems (Nyon, Switzerland)	25
Epos Ultra	F-EH	Dornier MedTech (Wessling, Germany)	11
Sonocur	F-EM	Siemens (Erlangen, Germany)	11
Minilith SL 1	F-EM	Storz Medical (Tägerwil, Switzerland)	10
Modulith SLK	F-EM	Storz Medical	9
Ossatron	F-EH	HMT (Kreuzlingen, Switzerland)	7
Osteostar	F-EM	Siemens	7
Duolith SD1 focused	F-EM	Storz Medical	5
Orthospec	F-EH	Medispec (Yehud, Israel)	4
Physio SW Therapy	R	Pagani (Paderno Dugnano, Italy)	3
BTL-5000	R	BTL (Prague, Czech Republic)	2
EvoTron	F-EH	HMT	2
JEST-2000	R	Joemedical (Daejeon, Korea)	2
Masterpuls MP 100	R	Storz Medical	2
Orthima	F-EM	Direx (Petah Tikva, Israel)	2
Piezoon 100	F-PE	Richard Wolf (Knittlingen, Germany)	2
Piezoon 300	F-PE	Richard Wolf	2
Piezowave	F-PE	Richard Wolf	2
Stonelith V5		PCK (Ankara, Turkey)	2
Compact	F-EM	Dornier	1
Duolith SD1 radial	R	Storz Medical	1
Lithostar	F-EM	Siemens	1
MedTech Epos	F-EM	Dornier	1
MFL 5000	F-EH	Phillips (Eindhoven, Netherlands)	1
Masterpuls MP 200	R	Storz Medical	1
Orthowave	F-EH	MTS	1
Piezolith 2501	F-PE	Richard Wolf	1
ShockMaster	R	Gymna (Bilzen, Belgium)	1

R, radial; F-EH, focused-electrohydraulic; F-EM, focused-electromagnetic; F-PE, focused-piezoelectric.

## **2. Hypothesis**

Based on the results of the systematic literature search outlined above it is hypothesized here that rESWT using the Swiss DolorClast is effective and safe in treatment of non-specific low back pain.

Because the majority of patients with non-specific low back pain presenting to the Department of Pain Medicine at the First Affiliated Hospital of Zhejiang University, Hangzhou are suffering from chronic non-specific low back pain, the proposed project will be restricted to the treatment of chronic non-specific low back pain.

The standard therapy of chronic non-specific low back pain at the Department of Pain Medicine at the First Affiliated Hospital of Zhejiang University consists of the non-steroidal anti-inflammatory drug Celecoxib (200 mg per day) and the antispasmodic drug Eperisome (50 mg per day) (henceforth abbreviated to as C-E drug therapy). Considering the established evidence of superiority of combination therapies of rESWT performed with the Swiss DolorClast and other treatment modalities (such as the combination of rESWT and plantar fascia-specific stretching in case of chronic plantar fasciopathy; Rompe et al., 2015; and the combination of rESWT and eccentric loading in case of chronic midportion Achilles tendinopathy; Rompe et al., 2009) the proposed study will specifically test the hypothesis that rESWT performed with the Swiss DolorClast in combination with C-E drug therapy is statistically significantly more effective than either rESWT or C-E drug therapy alone in the treatment of chronic non-specific low back pain.

## **3. Study Objectives**

### **3.1. General Objective**

- 1) To determine the efficacy and safety of rESWT in combination with C-E drug therapy in treatment of chronic non-specific low back pain.

### **3.2. Specific Objectives**

- 1) To determine the efficacy of combined rESWT /C-E drug therapy, rESWT alone and C-E drug therapy alone in treatment of chronic non-specific low back pain.
- 2) To evaluate patient's pain score, Oswestry Disability Index score, Clinical Global Impression score, and anxiety and depression score (including GAD-7, PHQ-9, PHQ-15 and pain disaster score) at baseline and at two weeks, four weeks, 12 weeks and 24 weeks after baseline.

- 3) To evaluate patient's lumbar curvature using lateral X-ray radiographs at baseline and at 12 weeks after baseline.
- 4) To evaluate patient's cross-sectional area of the paravertebrate muscles using MRI at baseline and at 12 weeks after baseline.
- 5) To evaluate safety of rESWT in treatment of chronic non-specific low back pain.

## 4. Study protocol

### 4.1. Introduction

An advanced study design of a clinical trial is ways more than just to decide how many patients will be treated with treatment X and how many patients with treatment Y, and how treatments X and Y should be performed. Actually an advanced study design of a RCT has to consider everything that will be checked later in assessments of the methodological quality of a RCT of health care interventions. There are at least six different assessments available:

1. Jadad et al. (1996) – This is a very basic assessment, attributing to each RCT a quality score out of a maximum of six points: (1) Was the generation of randomization sequence described? (2) Was the method of allocation concealment described? (3) Was an intention to treat analysis used? (4) What number of patients was lost to follow-up? (5) Was the outcome assessment blind? and (6) Was the patient blind to treatment allocation? The design of the proposed study on rESWT for chronic soft tissue wounds considers all these aspects.
2. The DELPHI list (Verhagen et al., 1998) – The DELPHI list consists of the following questions: (1) Was a method of randomization performed? (2) Was the treatment allocation concealed? (3) Were the groups similar at baseline regarding the most important prognostic indicators? (4) Were the eligibility criteria specified? (5) Was the outcome assessor blinded? (6) Was the care provider blinded? (7) Was the patient blinded? (8) Were point estimates and measures of variability presented for the primary outcome measures? (9) Did the analysis include an intention-to-treat analysis? The design of the proposed study on rESWT for chronic soft tissue wounds considers all these aspects, except of the fact that the care providers will not be blinded.
3. The PEDro scale (Blobaum, 2006) (outlined in detail in Section 1 above) - This scale is a development of the DELPHI list and consists of a total of 10 scale items, including random allocation, concealment of allocation, comparability of groups at baseline, blinding of patients, therapists and assessors, analysis by intention to treat and adequacy of follow-up,

between-group statistical comparisons, and reports of both point estimates and measures of variability. The design of the proposed study on rESWT for chronic non-specific low back pain considers all these aspects, except of the fact that patients and therapists will not be blinded (which is in principle not possible when comparing combined ESWT /C-E drug therapy with ESWT alone and C-E drug therapy alone).

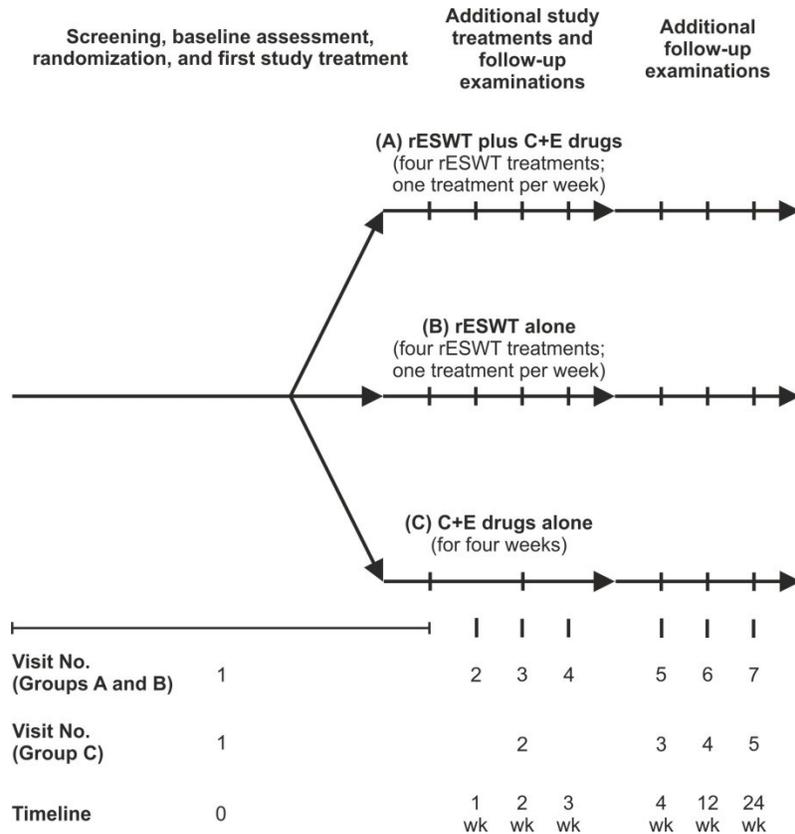
4. Chalmers et al. (1981) – This assessment consists of two evaluation forms that include 29 individually scored items, allowing a maximum score of 100.
5. Downs and Black (1998) – This assessment includes 27 individually scored items, allowing a maximum score of 32.
6. The CONSORT statement (Schulz et al., 2010) – The CONSORT statement is intended to improve the reporting of RCTs, enabling readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results.

The assessments of Chalmers et al. (1981), Downs and Black (1998) and Schulz et al. (2000) are very similar. However, Downs and Black (1998) provide the most specific questions. Accordingly, the design of the proposed study on rESWT for chronic non-specific low back pain was developed according to the criteria set out by Downs and Black (1998). The proposed study on rESWT for chronic non-specific low back pain will achieve a very high rating on the assessment by Downs and Black (1998).

#### **4.2. Study design**

- Randomized controlled trial (RCT), no blinding of patients and therapists applying the treatments (the rationale for this is provided in Section *Blinding of therapists and assessors* below, there will be blinding of evaluators/assessors).

### 4.3. Schematic diagram of study design:



### 4.4. Inclusion criteria

- Adults (both male and female) with non-specific low back pain for more than three months.
- Age range: between 18 and 80 years.
- Willingness of the patient to participate in the study, and written informed consent signed and personally dated by the patient.
- Chronic non-specific low back pain clinically diagnosed as repeated lumbar sourness and swelling pain or a chronic progressive process, accompanied by (i) X-ray examination to exclude lumbar vertebrate fractures, spondylolysis, spondylolisthesis and severe osteoporosis, and/or (ii) MRI with normal signal or low nucleus pulposus signal.
- No contraindications for rESWT.

### 4.5. Exclusion criteria

- Children and teenagers below the age of 18.

- Elderly aged >80 years old
- No willingness of the patient to participate in the study, and/or written informed consent not signed and not personally dated by the patient.
- Previous spinal fracture or spinal surgery.
- Protrusion of a lumbar intervertebral disk, ankylosing spondylitis, scoliosis, lumbar spondylolisthesis and lumbar spondylolysis.
- Systemic disorders and psychiatric disorders.
- Contraindications of C-E drug treatment, including:
  - treatment of patients allergy to celecoxib, eprisome or sulfonamides,
  - patients with gastrointestinal bleeding or bleeding history,
  - patients with renal dysfunction,
  - patients with severe heart failure, and
  - lactating women.
- Contraindications of rESWT:
  - treatment of pregnant patients,
  - treatment of patients with blood-clotting disorders (including local thrombosis),
  - treatment of patients treated with oral anticoagulations,
  - treatment of patients with local tumors,
  - treatment of patients with local bacterial and/or viral infections (including lumbar vertebral tuberculosis), and
  - treatment of patients treated with local corticosteroid applications in the time period of six weeks before the first rESWT session (if applicable).
- Participation in any other clinical trial in the time period of 12 weeks before potential inclusion in the proposed study.

#### **4.6. Groups and treatments**

Patients in the rESWT plus C-E drugs group will receive the below:

- Celecoxib (1 × 200 mg per day for moderate pain [NRS 4-6; c.f. Section 4.11.2 below] or 2 × 200 mg per day [NRS 7-10]) for four weeks.
- Eperisome (3 × 50 mg per day) for four weeks.
- Four rESWT sessions with the Swiss Dolorclast and the EvoBlue handpiece, as follows:
  - One rESWT session per week.

- 4 × 1000 rESWs per session (1000 rESWs each applied to the left and the right paravertebrate muscles above L3 to S1 using the 36-mm applicator, plus 1000 rESWs each applied to the left and the right sacroiliacal joint using the 15-mm convex applicator, in prone position of the patient).
- rESWs applied at 15 Hz
- Air pressure of the Swiss DolorClast (and, thus, the energy flux density of the applied rESWs) gradually increased during the first 200 rESWs each until the maximum discomfort the patient can tolerate will be reached, followed by 800 rESWs at this air pressure / energy flux density.
- No application of local anaesthetics (Rompe et al., 2005; Schmitz et al., 2013; 2015).

Patients in the rESWT group will receive the below:

- Four rESWT sessions with the Swiss Dolorclast and the EvoBlue handpiece as described above for the *rESWT plus C-E drugs* group.

Patients in the C-E drugs group will receive the below:

- Celecoxib and Eperisome as described above for the *rESWT plus C-E drugs* group.

In addition, all patients will be advised to perform simplified, safe core stability training and flexion relaxation training at home, which is mainly based on the contraction of the lumbar muscles, under the guidance of a unified rehabilitation training video (two training sessions per week; each training session lasting for approximately 20 minutes; training for 24 weeks).

#### **4.7. Recruitment of patients**

- Patients in the *rESWT plus C-E drugs* group, the *rESWT* group and the *C-E drugs* group will be selected from the same hospital (Department of Pain Medicine at the First Affiliated Hospital of Zhejiang University), and will be recruited over the same period of time.
- Recruitment of patients will start immediately after approval of the study by the Medical Research and Ethics Committee of the First Affiliated Hospital of Zhejiang University.
- Patients will be recruited during regular visits to the Department of Pain Medicine at the First Affiliated Hospital of Zhejiang University. All potential patients that fulfill the inclusion criteria and do not fulfill any of the exclusion criteria outlined above will be offered to participate in the proposed study until the total number of patients (*rESWT plus C-E drugs* group: n=50; *rESWT* group: n=50; *C-E drugs* group: n=50) will be recruited. Accordingly, the subjects that

will be prepared to participate in the proposed study will be representative of the entire population from which they were recruited. We will report the proportion of those asked who agreed.

- The intervention will be undertaken in a specialist centre that is representative of the hospitals in China most of the source population would attend if seeking treatment of chronic non-specific low back pain.

#### **4.8. Informed Consent Process**

Should patients agree to be part of the proposed study, they will be guided through the informed consent process first, as described here. The Informed Consent Process will be done at the Department of Pain Medicine at the First Affiliated Hospital of Zhejiang University. A copy of the Participant Information Sheet will be given to them. The patient will be given sufficient time to read and understand everything written on the document. The Principal Investigator will be there to explain and answer any queries that may arise. The patient will sign the Informed Consent Form if agreeable thereafter.

#### **4.9. Randomization and blinding of patients**

- Patients that fulfill the inclusion criteria and do not fulfill any of the exclusion criteria will be randomly allocated to either rESWT plus C-E drugs (n=50), rESWT alone (n=50) or C-E drugs alone (n=50), respectively (sample size is addressed in Section 5.1. *Power analysis* below).
- Randomization will be performed as described by Rompe et al. (2008) in a randomized, controlled study on rESWT for Achilles tendinopathy. Specifically, a computerized random-number generator will be used to formulate an allocation schedule. Subjects will be randomized to either treatment (rESWT plus C-E drugs, rESWT alone or C-E drugs alone), with use of the method of randomly permuted blocks. The randomization scheme will be generated with the use of the website [www.randomization.com](http://www.randomization.com). One hundred and fifty patients will be randomized into five blocks. A medical assistant at the Department of Pain Medicine at the First Affiliated Hospital of Zhejiang University will allocate interventions by means of opaque sealed envelopes that will be marked according to the allocation schedule. The medical assistant will be unaware of the size of the blocks.
- The randomized intervention assignment as outlined above will be concealed from both patients and health care staff until recruitment will be complete and irrevocable.

- Neither patients nor therapists will be blinded in the proposed study. The therapist will be the person who will administer rEWST to the patient.
- The assessor will be blinded in the proposed study. The assessor is the person who will assess treatment success during follow up.

#### **4.10. Study treatment and visits**

Study visits of patients in the *rESWT plus C-E drugs* group and the *rESWT* group will take place at 0, 1, 2 and 3 weeks for administering rESWT. A single study visit of patients in the *C-E drugs* group will take place at 0 weeks.

In addition,

- at two weeks (i.e., after two rESWT sessions and immediately before the third rESWT session in case of patients in the *rESWT plus C-E drugs* group and the *rESWT* group),
- four weeks (i.e., one week after the last rESWT session in case of patients in the *rESWT plus C-E drugs* group and the *rESWT* group)
- 12 weeks and
- 24 weeks after baseline

treatment outcome will be evaluated (separate visits at four weeks, 12 weeks and 24 weeks after baseline in case of patients in the *rESWT plus C-E drugs* group and the *rESWT* group, as well as separate visits at two weeks, four weeks, 12 weeks and 24 weeks after baseline in case of patients in the *rESWT* group).

The investigator will perform the following procedures at the first visit:

- check eligibility,
- obtain informed consent,
- perform randomization, and
- collect patient's demographics & medical history.

Furthermore, the investigator will perform the following procedures at all visits:

- record any concomitant medication,
- perform clinical examination,
- report adverse events (AE) and serious adverse events (SAE), and
- complete relevant section of case report form (CRF)

Study visits and procedures are summarized in Tables 5 and 6 below.

**Table 5.** Study visits and procedures planned for the *rESWT plus C-E drugs* group and the *rESWT* group

	Screening, baseline assessment, randomization and first treatment	Additional study visits and follow-up examinations				Additional follow-up examinations	End
Visit	1	2	3	4	5	6	7
Timeline	0	1 wk	2 wks	3 wks	4 wks	12 wks	24wks
<b>Procedures</b>							
Check eligibility	X						
Obtain informed consent	X						
Perform randomization	X						
Collect patient's demographics & medical history	X						
Record any concomitant medication	X	X	X	X	X	X	X
Perform clinical examination	X	X	X	X	X	X	X
Dispense rESWT	X	X	X	X			
Perform efficacy assessment					X	X	X
Report AE and SAE	X	X	X	X	X	X	X
Complete relevant section of CRF	X	X	X	X	X	X	X

**Table 6.** Study visits and procedures planned for the *C-E drugs* group

	Screening, baseline assessment, randomization and first treatment	Follow-up examinations			End
Visit	1	2	3	4	5
Timeline	0	2 wks	4 wks	12 wks	24wks
<b>Procedures</b>					
Check eligibility	X				
Obtain informed consent	X				
Perform randomization	X				
Collect patient's demographics & medical history	X				
Record any concomitant medication	X	X	X	X	X
Perform clinical examination	X	X	X	X	X
Perform efficacy assessment		X	X	X	X
Report AE and SAE	X	X	X	X	X
Complete relevant section of CRF	X	X	X	X	X

#### 4.11. Outcome of Interest

##### 4.11.1. Primary clinical outcome and definition of treatment success

- Primary clinical outcome will be the Pain Self-Efficacy Questionnaire (PSEQ) score (Nicholas, 1989).
  - Patients will be asked to rate how confident they are at the time of examination despite the presence of their pain in performing the following activities, listed by selecting a number on a 7 point scale where 0 equals “not at all confident” and 6 equals “completely confident”:
    - I can enjoy things, despite the pain.

- I can do most of the household chores (e.g. tidying-up, washing dishes, etc.), despite the pain.
- I can socialize with my friends or family members as often as I used to do, despite the pain.
- I can cope with my pain in most situations.
- I can do some form of work, despite the pain (“work” includes housework, paid and unpaid work).
- I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite the pain.
- I can cope with my pain without additional medication (next to rESWT plus C-E drugs, rESWT alone or C-E drugs alone, respectively).
- I can still accomplish most of my goals in life, despite the pain.
- I can live a normal lifestyle, despite the pain.
- I can gradually become more active, despite the pain.
- Scores on the PSEQ may range from 0 to 60, with higher scores indicating stronger self-efficacy beliefs.
- A point score change of 11 points for the PSEQ score corresponds to the minimal clinically important difference (MCID), defined as the smallest difference that patients and clinicians perceive to be worthwhile when treating chronic non-specific low back pain (Maughan and Lewis, 2010).
- According to Maughan and Lewis (2010) the PSEQ score is responsive to clinically important change over time.
- The PSEQ score will be collected at baseline and at all follow-up examinations, i.e., two weeks, four weeks, 12 weeks and 24 weeks after baseline.
- In the present study treatment success is defined as individual improvement of the PSEQ score by more than 20 points at 12 weeks after baseline.

#### **4.11.2. Secondary clinical outcomes**

Secondary clinical outcomes will be:

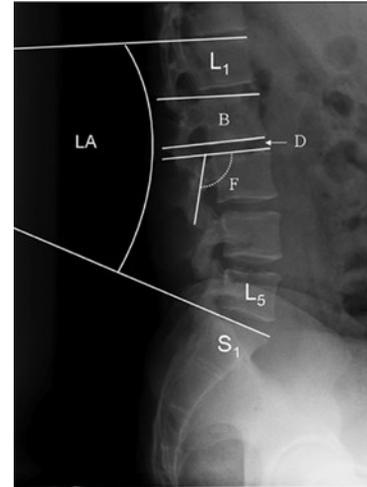
- Numerical Rating Scale (NRS) score - The NRS will ask patients to rate their pain intensity on an 11-point scale where 0 indicates no pain and 10 indicates worst imaginable pain. The NRS score will be collected at baseline and at all follow-up examinations, i.e., two weeks, four weeks, 12 weeks and 24 weeks after baseline. A point score change of 4 points for the NRS score corresponds to the MCID (Maughan and Lewis, 2010). Note that according to

Maughan and Lewis (2010) the NRS score is least responsive in measuring clinically meaningful change in a chronic non-specific low back pain population.

- Oswestry Low Back Pain Disability Questionnaire (OLDPDQ) score (Fairbank and Pynsent, 2000; Davidson and Keating, 2001) – The OLDPDQ score is considered the ‘gold standard’ of low back functional outcome tools. The questionnaire is composed of ten sections (addressing pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life and travelling); for each section the possible score is 5 and, thus, the total possible score is 50. The final score is calculated as  $[(\text{sum of individual scores}) / 50] * 100$  (%), and is interpreted as *minimal disability* (0% to 20%), *moderate disability* (21% to 40%), *severe disability* (41% to 60%), *crippled* (61% to 80%) or *patients are either bed-bound or exaggerating their symptoms* (81% to 100%). The OLDPDQ score will be collected at baseline and at all follow-up examinations, i.e., two weeks, four weeks, 12 weeks and 24 weeks after baseline. A point score change of 8 points for the OLDPDQ score corresponds to the MCID (Maughan and Lewis, 2010).
- Patient Health Questionnaire 9 (PHQ-9) score (Kroenke et al., 2001) – The PHQ-9 will be used to assess depression. Patients will be asked how often, over the last two weeks, they had been bothered by the following problems: (i) little interest or pleasure in doing things; (ii) feeling down, depressed or hopeless; (iii) trouble falling or staying asleep, or sleeping too much; (iv) feeling tired or having little energy; (v) poor appetite or overeating; (vi) feeling bad about themselves, or that they are a failure or have let themselves or their family down; (vii) trouble concentrating on things, such as reading the newspaper or watching television; (viii) moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that they have been moving around a lot more than usual; and (ix) thoughts that they would be better off dead or of hurting themselves in some way. For each potential problem the PHQ-9 score uses a 4-point scale where 0 = not at all, 1 = several days, 2 = more than half the days and 3 = nearly every day. The PHQ-9 score will be collected at baseline and at 12 weeks and 24 weeks after baseline.
- Lumbar curvature measurements performed on lateral lumbosacral spine radiographs – Chun et al. (2017) found a strong relationship between non-specific low back pain and decreased lumbar lordotic curvature in a recent meta-analysis based on 13 studies consisting of 796 patients suffering from non-specific low back pain and 927 healthy controls. Lateral X-rays of the lumbar spine will be taken in the standing position according to standard protocols in the literature (e.g., Chernukha et al., 1976; Marks et al., 2009; Been and Kalichman, 2014) and analyzed using Cobb’s angle, vertebral body and intervertebral

disc wedging, and facet joint angle (Fig. 3) (e.g., Been and Kalichman, 2014). Lumbar curvature measurements will be performed at baseline and at 12 weeks after baseline.

**Fig. 3** (taken from Been and Kalichman, 2014). Measurements of lumbar lordosis Cobb's angle (LA), vertebral body (B) and intervertebral disc (D) wedging, and facet joint angle (F).



#### 4.12. Blinding of therapists and assessors

- Therapists applying the treatments will not be blinded. This will be done because even when using coded “active” and “placebo” handpieces in a study on ESWT, blinding of ESWT therapists can only be achieved when another person prepares the device before rESWT or sham treatment. This, however, is almost impracticable and has not been done in any of the more than 100 studies on rESWT and fESWT listed in the PEDro database (Schmitz et al., 2015). The solution to this issue is a strict, standardized way of interaction between the ESWT therapist and the patients, irrespective of treatment allocation (as mentioned in a study by Buchbinder et al., 2002). This approach will also be applied in the proposed study.
- All assessments before the first treatment (baseline) and during the follow-up period will be performed by assessors blind to the intervention.

## 5. Follow-up and statistical analysis

- Follow-up will be the same for all study patients.
- The design of the proposed study guarantees that there will be full compliance with the allocated treatment and, thus, no contamination of one group.
- The patient's age, gender, body mass index, job occupation and duration of non-specific low back pain are potential confounding factors when treating chronic non-specific low back pain with rESWT. Normal distribution of these data will be tested using the D'Agostino-Pearson omnibus test. In case of passing the normality test we will report mean and standard error of the mean of these variables; otherwise we will report inter-quartile ranges of these variables. Comparison between groups will be performed with ANOVA followed by Bonferroni post tests for pairwise comparisons in case of passing the normality test, or the nonparametric Kruskal-Wallis test followed by Dunns tests for pairwise comparisons in case of not passing the initial normality test.
- As outlined in Section "Primary clinical outcome and definition of treatment success" above, the primary clinical outcome will be the PSEQ score at 12 weeks after baseline. Treatment success (i.e., number of patients with individual improvement of PSEQ score by more than 20% at 12 weeks after baseline) will be tested with Fisher's exact test.
- As outlined in Section "Secondary clinical outcomes" above, the secondary clinical outcomes will be the NRS score, OLDPDQ score, PHQ-9 score, Cobb's angle, vertebral body and intervertebral disc wedging and facet joint angles. Each secondary clinical outcome will return a single data point at each time of follow-up examination. The NRS score, OLDPDQ score and PHQ-9 score are not normally distributed data. Accordingly, we will report inter-quartile ranges of these variables. Comparison between groups will be performed using the nonparametric Kruskal-Wallis test followed by Dunns tests for pairwise comparisons. Normal distribution of the Cobb's angle, vertebral body and intervertebral disc wedging and facet joint angles will be tested using the D'Agostino-Pearson omnibus test. Comparison between groups will be performed with ANOVA followed by Bonferroni post tests for pairwise comparisons in case of passing the normality test, or the nonparametric Kruskal-Wallis test followed by Dunns tests for pairwise comparisons in case of not passing the initial normality test.
- The probability value of less than 0.05 ( $p\text{-value} < 0.05$ ) will be considered as statistically significant (Lang & Secic, 2006).

- All calculations will be performed using GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego, CA, USA).
- All main conclusions of the study will be based on analyses of intention to treat rather than analyses of treatment. Note that there are various available methods for handling missing data in clinical trials (European Medicines Agency, 2010). In case of missing data (i.e., in case a patient will withdraw or will be lost during the treatment or the follow-up periods) we will determine together with the statistics experts at the Institute for Medical Informatics, Biometry and Epidemiology (IBE) at the Ludwig-Maximilians-University of Munich (Munich, Germany) the most appropriate method for performing analyses of intention to treat. After randomization and the first treatment with respectively rESWT plus C-E drugs, rESWT alone or C-E drugs alone, no patient will be replaced.
- All efforts will be made to keep the proportion of patients lost to follow-up too small to affect the main findings of the proposed study.
- Patient-centered care throughout the proposed study will ensure that no patients will be lost to follow-up, or the number of patients lost to follow-up will be so small that findings would be unaffected by their inclusion.
- We will report actual probability values for all outcomes except where probability values less than 0.001 are found.
- We will avoid any retrospective unplanned subgroup analysis and, thus, “data dredging”.

### **5.1. Power analysis**

In none of the studies on ESWT for non-specific low back pain performed so far (Nedelka et al., 2014; Lee et al., 2014; Han et al., 2014; Moon et al., 2016) a definition of treatment success was defined, a Power analysis was reported and the PSEQ score was used to assess clinical outcome. Accordingly, these studies are only of very limited use for the purpose of performing a Power analysis of the proposed study.

Based on anecdotal evidence from several therapists in Europe and Latin America who have been using rESWT for non-specific low back pain for more than a decade we hypothesize that treatment of chronic non-specific low back pain with rESWT alone as described above will result in a success rate of approximately 70%, and the combination of rESWT and C-E drugs in a success rate of approximately 85%. Furthermore, based on our own experience we hypothesize that treatment of chronic non-specific low back pain with C-E drugs alone as described above will result in a success rate of only approximately 35%

On this basis we performed a Power analysis, both for a percentage of 35% as well as for various other percentages (ranging between 10% and 99.9%) of patients with treatment success when treated with C-E drugs alone, accounting for a two sided-confidence interval of 95% (and, thus, a type-1 error rate of 5%). Calculations were performed using the software Open Source Epidemiologic Statistics for Public Health ([www.openepi.com](http://www.openepi.com)). The results are summarized in Tables 7 and 8.

**Table 7.** Power for the proposed RCT on rESWT plus C-E drugs or rESWT alone for chronic non-specific low back pain, accounting for a two sided-confidence interval of 95% and a percentage of patients with treatment success of 40% when treated with C-E drugs alone (assuming n=50 patients per group).

Percent of patients treated with rESWT plus C-E drugs or C-E drugs alone with treatment success [%]	Power based on Normal approximation [%]	Power based on Normal approximation with continuity correction [%]
99.9	100	100
90	100	100
<b>85</b>	<b>100</b>	<b>100</b>
80	99.8	99.6
<b>70</b>	<b>95.0</b>	<b>92.4</b>
60	71.3	63.5
50	32.7	25.2
40	7.2	3.5
35	1.1	0

**Table 8.** Power for the proposed RCT on rESWT plus C-E drugs for chronic non-specific low back pain, accounting for a two sided-confidence interval of 95% and a percentage of patients with treatment success of 70% when treated with rESWT alone (assuming n=50 patients per group).

Percent of patients treated with rESWT plus C-E drugs or C-E drugs alone with treatment success [%]	Power based on Normal approximation [%]	Power based on Normal approximation with continuity correction [%]
99.9	99.3	98.3
90	71.2	61.2
<b>85</b>	<b>43.4</b>	<b>33.4</b>
80	20.9	14.2
70	1.1	0

Furthermore, we calculated the minimum sample size in both groups (rESWT, control) that would be necessary for detecting a difference in treatment success between

- the patients treated with rESWT plus C-E drugs and the patients treated with C-E drugs alone,
- the patients treated with rESWT alone and the patients treated with C-E drugs alone, and

- the patients treated with rESWT plus C-E drugs and the patients treated with C-E drugs alone,

accounting for a two sided-confidence interval of 95% and a power of 0.8. Calculations were also performed using the software Open Source Epidemiologic Statistics for Public Health ([www.openepi.com](http://www.openepi.com)). The results are summarized in Tables 9 and 10.

**Table 9.** Sample size in the proposed RCT on rESWT plus C-E drugs or rESWT alone for chronic non-specific low back pain, accounting for a two sided-confidence interval of 95% and a power of 0.8. The percentage of patients with treatment success when treated with C-E drugs alone was set at 40%.

Sample size of both groups (rESWT, placebo) according to...				
Percent of patients with treatment success when treated with rESWT plus C-E drugs or rESWT alone [%]	Kelsey et al. (1996)	Fleiss et al. (2003)	Fleiss et al. (2003) with continuity correction	
99.9	10	8	11	
90	15	14	17	
<b>85</b>	<b>19</b>	<b>17</b>	<b>22</b>	
80	24	23	28	
<b>70</b>	<b>44</b>	<b>42</b>	<b>49</b>	
60	99	97	107	
50	389	388	408	
45	1502	1501	1540	

**Table 10.** Sample size in the proposed RCT on rESWT plus C-E drugs for chronic non-specific low back pain, accounting for a two sided-confidence interval of 95% and a power of 0.8. The percentage of patients with treatment success when treated with rESWT alone was set at 70%.

Sample size of both groups (rESWT, placebo) according to...				
Percent of patients with treatment success when treated with rESWT plus C-E drugs or rESWT alone [%]	Kelsey et al. (1996)	Fleiss et al. (2003)	Fleiss et al. (2003) with continuity correction	
99.9	23	22	28	
90	63	62	72	
<b>85</b>	<b>122</b>	<b>121</b>	<b>134</b>	
80	297	296	316	
75	1221	1220	1259	

In summary, the proposed study has a power of more than 0.8 in finding a difference in treatment success (individual improvement of the PSEG score by more than 20 points at 12 weeks after baseline) between rESWT plus C-E drugs and C-E drugs alone, as well as between rESWT alone and C-E drugs alone, for treating chronic non-specific low back pain when randomizing at least 49 patients into each group.

On the other hand, the proposed study does not have a power of more than 0.8 in finding a difference in treatment success (individual improvement of the PSEG score by more than 20 points at 12 weeks after baseline) between rESWT plus C-E drugs and rESWT alone, for treating chronic non-specific low back pain when randomizing less than 134 patients into each group.

In summary, the proposed study can test the following hypotheses in the treatment of chronic non-specific low back pain: (i) rESWT plus C-E drugs is superior to C-E drugs alone, and (ii) rESWT alone is superior to C-E drugs alone. Furthermore, the proposed study can retrieve important pilot data for designing a follow-up study testing the hypothesis that rESWT plus C-E drugs is superior to rESWT alone in the treatment of chronic non-specific low back pain.

Collectively, the results of the Power analysis reinforce the validity of the proposed study protocol for testing efficacy and safety of rESWT using the Swiss DolorClast for chronic non-specific low back pain.

## **6. Patient protection procedures**

### **6.1. Procedures in the event of Adverse Events**

- Potential unwanted side effects of rESWT may be petechial bruises of the skin at the treatment side and temporary numbness. These unwanted side effects normally vanish within one or two days.
- Potential unwanted side effects of celecoxib and Eperisome are increasing the risk of cardiovascular events and gastrointestinal events, exhaustion, dizziness.
- Should any unwanted side effects persists for longer than usual, the investigators will treat these patients according to usual standard of care of the First Affiliated Hospital of Zhejiang University.

### **6.2. Procedures in the event of Emergency**

The principal investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study.

### **6.3. Procedures in the event of Pregnancy**

The subject must be instructed to inform the investigator if she becomes pregnant during the study. As pregnancy is a contraindication for treatment with rESWT, the patient will be

terminated from the study. The investigator will follow up the pregnancy until the outcome is known.

#### **6.4. Patient data protection**

Subjects' anonymity will be maintained. In order to guarantee confidentiality of records and documents that could identify subjects, subjects will only be identified by their assigned identification number on all case report forms (CRFs) and other records and documents. The investigator will keep a Patient Identification List with complete identification information (identification number, name, address, contact number) on each subject. Documents not for submission to the Medical Research and Ethics Committee of the First Affiliated Hospital of Zhejiang University and/or the Chinese Clinical Trial Register such as subject's written informed consent form will be maintained by the investigator in strict confidence.

#### **6.5. Insurance**

With respect to any liability directly or indirectly caused by the investigational products in connection with the proposed study, the principal investigator and the Department of Pain Medicine at the First Affiliated Hospital of Zhejiang University assumes liability by law for possible injury to the subject. The investigator and his/her staff will strictly follow the instructions of the manufacturer of the rESWT device Swiss DolorClast (Electro Medical Systems; Nyon, Switzerland) in accordance with the proposed protocol and any amendments thereto. Furthermore, the investigator and his/her staff will in general perform the proposed study in accordance with scientific practice and currently acceptable techniques and know how.

#### **6.6. Rescue medication/procedure**

rESWT itself does not require specific rescue medication / procedures.

### **7. Study Termination/Suspension**

The principal investigator holds the right to suspend or terminate patient's participation in the proposed study in the event of deterioration of clinical condition at the discretion of the investigator.

#### **7.1 Subject Withdrawal & Drop-out**

Subjects are free to withdraw from the study at any time for any reason.

Subjects may also be withdrawn from the study at any time at the discretion of the investigator. Should a subject withdraw or is withdrawn, every effort will be made to complete and report the observations as thoroughly as possible. Possible reasons for withdrawal will be documented. For e.g.:

- adverse event(s)
- abnormal laboratory values
- improvement of subject's condition such that he/she no longer requires study treatment
- insufficient therapeutic effect
- protocol violation (eg. incorrectly enrolled or randomised)
- subject requires use of unacceptable concomitant medication
- subject not compliant with protocol procedures
- subject develops a condition during the study that violates the inclusion/exclusion criteria
- lost to follow-up
- death
- any other reason, in the investigator's opinion, that would impede the subject's participation in the study

## **7.2. Procedures for handling withdrawal**

Subjects who withdraw or are withdrawn from the study will have the below information recorded:

- the reason(s) for their withdrawal,
- presence of any adverse events and if so will be followed up by regular scheduled visits, telephone contact and correspondence until satisfactory clinical resolution of adverse events is achieved,
- at least one follow-up contact (scheduled visit, telephone contact, correspondence) for safety evaluation during the 30 days following the last session of study treatment, and
- in the event of pregnancy, the subject should be monitored until conclusion of the pregnancy and the outcome of pregnancy reported.

## **7.3. Subject replacement policy**

After randomization and the first rESWT plus C-E drugs, rESWT alone or C-E drugs alone treatment, no patient will be replaced.

#### **7.4. Medications permitted or not permitted during the study.**

No other adjunct pharmacological treatment for non-specific low back pain is allowed during the duration of the study. Other medications not permitted are as explained in the Exclusion Criteria. Medications permitted are those not mentioned in the Exclusion Criteria.

### **8. Ethical Consideration**

The researchers have considered the ethical issues that may arise with the conduct of the proposed study. The proposed study will only be conducted after seeking approval from the Medical Research and Ethics Committee of the First Affiliated Hospital of Zhejiang University.

### **9. Subject Withdrawal & Compensation**

Participation in the proposed study is completely voluntary. The participants will not be paid for joining the proposed study nor will they be expected to pay to join the proposed study. Participants are able to withdraw themselves from the proposed study at any time without any reason and consequences to their follow-up treatment. Standard routine care will still be provided to them. The researchers hold the right to use any data collected until a participant would withdraw from the proposed study.

### **10. Adverse Events**

#### **10.1. Definitions**

##### **Adverse event (AE)**

Any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavourable and unintended sign, symptom, laboratory observation or disease temporally associated with the use of the investigational product, whether or not related to the investigational product.

The following should be reported as AE:

- treatment emergent symptoms which include:
  - medical conditions or signs or symptoms that were absent before starting study treatment, and

- medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment;
- abnormal laboratory values or tests that induce clinical signs or symptoms or require therapy;
- any adverse experience even if no drug has been administered, for example during run in or wash out phase of the study; and
- any doubtful event should be treated as an AE.

**Unexpected adverse event**

Any adverse event not reported in the safety section of the Investigator's Brochure or if the event is of greater frequency, specificity or severity.

**Serious adverse event (SAE)**

Any adverse event occurring that:

- results in death, or
- is a life threatening adverse experience defined as any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. Note that this does not include a reaction that had it occurred in a more severe form, it would have caused death, and/or
- results in subject hospitalization or prolongation of existing hospitalization.

The following hospitalizations are not considered to be SAEs:

- those planned before entry into the study,
- elective treatment for a condition unrelated to study indication or study treatment,
- those that occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria in SAE definition),
- parts of normal treatment or monitoring of the study indication and are not associated with any deterioration in condition,
- results in a significant or persistent disability or incapacity defined as any event that results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions,
- is a congenital anomaly or birth defect,
- is any instance of overdose, either accidental or intentional (suspected or confirmed), and/or

- is any other important medical event, based upon appropriate medical judgement, that may jeopardize the subject or may require medical or surgical intervention to prevent or avert one of the outcomes listed above.

## **10.2. Detecting and documenting AE**

Information about all AEs, whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other means, would be recorded on the Adverse Event Page of the CRF and followed up as appropriate.

Each AE will be described by:

### **a) Nature of AE**

This will be documented in terms of a medical diagnosis(es). When this is not possible, the AE will be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject.

### **b) Duration**

Start and end dates

### **c) Assessment of causality**

The investigator will attempt to explain each AE and assess its relationship, if any, to the study treatment. Causality should be assessed using the following definitions:

#### • Very likely

- The AE follows a reasonable temporal sequence from study treatment administration,
- abates upon discontinuation of study treatment, and
- reappears on repeated exposure (re-challenge).

#### • Probable

- The AE follows a reasonable temporal sequence from study treatment administration,
- abates upon discontinuation of study treatment, and
- cannot reasonably be explained by known characteristics of the subject's clinical state.

#### • Possible

- The AE follows a reasonable temporal sequence from study treatment administration,
- but could have been produced by the subject's clinical state or other mode of therapy administered to the subject.

• Doubtful

- The temporal association between study treatment and AE is such that the study treatment is not likely to have any reasonable association with the observed event.

• Very unlikely

- The AE is definitely produced by the subject's clinical state or other mode of therapy administered to the subject.

The degree of certainty with which an AE is attributed to study treatment or alternative cause like natural history of disease or concomitant treatment will be guided by the following considerations:

- time relationship between treatment and occurrence of AE,
- de-challenge and re-challenge information, if applicable,
- dose response relationships,
- lack of alternative explanations, i.e. no concomitant drug used and no other inter-current disease,
- reaction of similar nature being previously observed with the rESWT device Swiss DolorClast, and/or
- reaction having often been reported in literature for similar devices.

**d) Severity of AE**

- **Mild:** awareness of signs or symptoms, but they are easily tolerated.
- **Moderate:** enough discomfort to cause interference with usual activity.
- **Severe:** incapacitating, with inability to work or do usual activity.

**10.3. Reporting SAE**

Information about all SAE will be recorded on the Serious Adverse Event Section of the CRF. All events documented in the SAE form must be reported within 24 hours to the Medical Research and Ethics Committee of the First Affiliated Hospital of Zhejiang University.

Any death or congenital abnormality, if brought to the attention of the investigator within 6 months after cessation of study treatment, whether considered treatment related or not, should be reported to the Medical Research and Ethics Committee of the First Affiliated Hospital of Zhejiang University.

#### **10.4. Treatment and follow up of AE**

Treatment of any AE is at the sole discretion of the investigator. Subjects with AE will be followed up until the event has resolved or the condition has stabilized. Otherwise appropriate medical care will be arranged for the patient. Abnormal tests will be repeated until they return to baseline levels or an adequate explanation of the abnormality has been found.

#### **In the Event of Pregnancy**

A female subject must be stopped from the treatment and immediately inform the investigator if she becomes pregnant during the study. The medical monitor will be contacted immediately to break the blind. The investigator will counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject will continue until conclusion of the pregnancy.

Pregnancies will be formally reported as SAEs.

#### **10.5. Safety update**

Electro Medical Systems will notify investigators of all AEs that are serious or unexpected and very likely, probably or possibly related to the investigational product. The investigator must retain such notice with the Investigator's Brochure and immediately submit a copy of this information to the Medical Research and Ethics Committee of the First Affiliated Hospital of Zhejiang University. The Medical Research and Ethics Committee of the First Affiliated Hospital of Zhejiang University will then determine if the informed consent requires revision. The investigator should also comply with the procedures of the Medical Research and Ethics Committee of the First Affiliated Hospital of Zhejiang University for reporting any other safety information.

#### **10.6. Potential unwanted side effects**

Potential unwanted side effects of rESWT may be petechial bruises of the skin and temporary numbness at the side of treatment. These unwanted side effects normally vanish within one or

two days. In case of petechial bruises of the skin they will be photographed and documented in the patient's record. Temporary numbness will also be documented in the patient's record. In the exceptional case that these unwanted side effects would really persist for longer than one or two days, (i) the corresponding patient would no longer be treated with rESWT but would be kept in the study for follow-up analysis, (ii) petechial bruises would be treated with, e.g., ice until they disappear, and (iii) patients with persistent numbness would be presented to a neurologist.

## **11. Statement on Confidentiality**

All data collected from participants will not have any personal identifiers. They will instead be given a specific research ID to respect the privacy and confidentiality of participants. The principal investigator will keep a separate Patient Identification List with complete identification information (identification number, name, address, contact number) and randomization number on each subject. All data collected will be stored in a computer that is protected by a password at the Department of Pain Medicine at the First Affiliated Hospital of Zhejiang University. Only investigators and study team members will have access to the study data. This limits the access to study data to the minimum number of individuals necessary for quality control, audit and analysis. Participants will not be given access to any personal information and study data collected during the proposed study.

## **12. Data Protection**

All collected data will be stored in a computer that is protected by a password at the Department of Pain Medicine at the First Affiliated Hospital of Zhejiang University. Only investigators and study team members will have access to the study data. Study data will be stored for a duration of five (5) years after completion of the study. All data will be destroyed thereafter.

## **13. Publication Policy**

The investigators shall have the right to publish or permit the publication of any information or material relating to or arising from the proposed study. All study data will be reported in a collective manner without any personal identifiers to protect the confidentiality of the participants.

## **14. Conflict of Interest**

The rESWT equipment to be used in the proposed study (Swiss DolorClast) is purchased from Electro Medical Systems (Nyon, Switzerland).

Dr. Christoph Schmitz serves as paid consultant for and receives benefits from Electro Medical Systems. However, Electro Medical Systems will have no any role in patient recruitment, treatment of patients, data collection and analysis, decision to publish, or preparation of corresponding manuscripts. Furthermore, Dr. Christoph Schmitz will have no any role in patient recruitment, treatment of patients and data collection.

No other potential conflicts of interest relevant to the proposed study were reported.

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