Crying, unsettled and distressed infants: Swiss arm of an international randomised controlled trial to test the effectiveness of osteopathic care

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category A
Study Registration:	ACTRN12620000047998 Ethical Multicentric approval obtained from the NHS in November 2019 under the registration number 19/LO/1620 Registration number from the FOPH portal SNCTP (Swiss National Clinical Trial Portal): To be added after ethical approval has been provided.
Main Sponsor:	Steve Vogel, University College of Osteopathy, 275 Borough High Street, London SE1 1JE, Steven.Vogel@uco.ac.uk, +44 20 7089 5331
Swiss Sponsor:	Nataly Viens Python, School of Health Sciences Fribourg, Rue des Arsenaux 16a, CH-1700 Fribourg, Nataly.ViensPython@hefr.ch, +41 26 429 60 05
Chief Investigator	Prof. Dawn Carnes, 275 Borough High St, London SE1 1JE dawn.carnes@uco.ac.uk, +44 7720 868 337
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Investigated Intervention:	The intervention under investigation is osteopathic manual therapy treatment for unsettled crying in infants. Treatment are given for approximately 10–20 minutes up to four times over two weeks. The treatment involves light osteopathic touch using techniques such as articulation, tension release (to ligaments, articular strains, fontanelles/cranial sutures), counter-strain/facilitated positional release, indirect functional techniques, myofascial release, soft tissue massage and/or stretch and visceral mouvement. Touch is directed at specific areas of the baby's body as deemed appropriate by the osteopath.
Protocol ID	IRAS_ID268925_CH_1.2
Version and Date:	Version 1.2 (dated 15/02/2021)

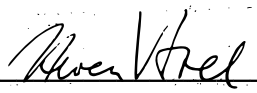
PROTOCOL SIGNATURE FORM

Study Title	Crying, unsettled and distressed infants: Swiss arm of an international randomised controlled trial to test the effectiveness of osteopathic care
Study ID	IRAS_ID268925_CH

The Main Sponsor and the Local Sponsor have approved the protocol version 1.2 (dated 15/02/2021) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Main Sponsor:

Name: *Steve Vogel, University College of Osteopathy, London, UK*

Date: 17.02.2021 Signature: 

Local Sponsor:

Name: *Nataly Viens Python, School of Health Sciences Fribourg, Fribourg, Switzerland*

Date: 16.03.2021 Signature: 

Chief Investigator:

Name: *Prof. Dawn Carnes, University College of Osteopathy, London, UK*

Date: 17.02.2021 Signature: 

Swiss Principal Investigator (Swiss study site):

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Principal Investigator: *Prof. Paul Vaucher*

Date: 15.02.2021 Signature: 

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR/DSUR	*Annual Safety Repot / Development Safety Report (CH)*
BASEC	*Business Administration System for Ethical Committees (CH)*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
DMC	*Data Monitoring Committee*
EU	*European Union*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health (CH)*
GCP	*Good Clinical Practice*
GLM	*Generalised linear model*
GTR	*Generic Tension Release (control arm)*
HES-SO	*University of Applied Sciences and Arts Western Switzerland (CH)*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
ICMJE	*International Committee of Medical Journal Editors*
ID	*Identification number*
ITT	*Intention-to-treat*
NAREG	*National Registry of Healthcare Professions (CH)*
NCOR	*National Council for Osteopathic Research (UK)*
NHS	*United Kingdom National Health Service (UK)*
NICE	*National Institute for Health and Care Excellence (UK)*
OMT	*Osteopathic Manipulative Treatment*
PI	*Principle investigator (national level)*
UCO	*University College of Osteopathy (UK)*
UK	*United Kingdom*
SD	*Standard deviation*
TMC	*Trial Management Committee*
TSC	*Trial Steering Committee*
TTR	*Targeted Tension Release (OMT arm)*
SAE	*Serious Adverse Event*

1 STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Main Sponsor: Steve Vogel, University College of Osteopathy, 275 Borough High Street, London SE1 1JE, Steven.Vogel@uco.ac.uk, +44 20 7089 5331 Swiss Sponsor: Nataly Viens Python, School of Health Sciences Fribourg, Rue des Arsenaux 16a, CH-1700 Fribourg, Nataly.ViensPython@hefr.ch, +41 26 429 60 05
Study Title	Crying, unsettled and distressed infants: Swiss arm of an international randomised controlled trial to test the effectiveness of osteopathic care
Short Title / Study ID	CUTIES-CH, IRAS_ID268925_CH
Protocol Version and Date	Version 1.1 (dated 07/01/2021) Linked to UK leading project and protocol IRAS_ID268925
Study Registration	Australian New Zealand Clinical Trials Registry: ACTRN12620000047998
Study Category and Rationale	Risk category A as the treatment under evaluation is usual osteopathic care already provided to the population with extremely rare observed associated severe adverse events that have always been related to use of excessive force and negligence. This study is to evaluate soft touch alone ruling out these risks altogether. The study is run from the UK and received ethical approbation in November 2019 (19/LO/1620). Ethical approbation for the Swiss arm was obtained in TO BE COMPETED.
Background and Rationale	Infants who excessively cry and are perceived as unduly distressed and unsettled may be otherwise healthy and thriving. However, these symptoms can have a marked impact on family life. Around 1 in 6 families are affected by excessive infant crying (Hiscock, Jordan 2004). It is associated with maternal issues such as depression, anxiety and loss of parenting confidence (Johnson et al 2015, Kurth et al 2010). The peak age for crying in infants, at week six, is the same as the peak age for severe infant injury or death as a result of abuse (Kato 2016, Berkowisz 2017). Health care resource use by parents is higher in an infant's first 6 months of life, indicating a greater need for support during this period (Johnson et al 2015). One of the major reasons for this increase includes unsettled infant behaviour and problems with sleeping and feeding (Morris et al., 2001). Many parents seek alternative care such as osteopathy for their 'colicky' infants. Osteopathic treatment for 'colicky' infants commonly involves gentle touch and movement (Prevost et al., 2019). Treatment includes gentle application of light tactile pressure to areas that are perceived to demonstrate palpably increased soft tissue tone. There is little evidence to support the mechanism of action underpinning this approach with the rationale for treatment theoretically driven. Leuchter et al., (2013) postulated that infants with colicky crying were less able to regulate their responses to everyday stimuli. This led to the hypothesis that osteopathic affective touch may be able to modulate stimuli produced within the gut and other internal organs (interoceptive stimuli) in a direction that reduced symptoms such as crying and distress (D'Alessandro et al., 2016, Cerritelli et al., 2017). Regardless of the physiological rationale or explanation for this approach, there is limited, low to moderate quality evidence to show that osteopathic and chiropractic care can help to reduce crying time in infants (Dobson et al., 2012; Carnes et al., 2018; Prevost et al., 2019). More scientifically robust definitive trials on the topic are needed to clarify the situation. Parents/carers are often in crisis when they seek support and care for their 'colicky' infants and that they expect the outcome of that care to have an almost immediate effect. Normally the symptoms of excessive crying, unsettledness and distress are self-limiting and start resolving around nine to 12 weeks of age (Wolke et al., 2017). This sudy is therefore designed to look at short-term impact of care on reducing crying time in infants with unsettled crying.
Risk / Benefit Assessment	The safety of manual therapy care in infants has been the subject of review (Carnes et al 2016, Dobson et al 2008). The reported incidence and prevalence of moderate and serious adverse events is very low with this form of gentle light touch therapy. Manipulation using manual thrust techniques are contra-indicated in this patient population and none will be used in this study. We expect this to be a very low risk of harm study in both arms of the trial especially as the treatment is very gentle and the condition is usually self-limiting and resolving.

Objective(s)	This study will explore whether targeted specific osteopathic light touch is superior to non-specific light touch in reducing average daily crying time over two weeks in unsettled crying infants. Secondary objectives are to measure effects on confidence in parenting skill, global impression of improvement, parent satisfaction, and cost of treatment.
Endpoint(s)	The primary outcome in the trial is the average daily crying time over 14 days measured by a daily diary completed by infant's parents. Secondary outcomes include average crying time over the first seven days, total crying time over 14 days, parent confidence in parenting skill at day 14, global impression of improvement at day 14, parent satisfaction and experience at day 14, adverse events data and basic direct cost of treatment.
Study Design	Single-blinded two-arm parallel pragmatic randomised multicenter international UK led clinical trial
Statistical Considerations	Differences in outcomes, eg. mean crying time, will be compared between groups using a multilevel mixed-effects generalised linear model (GLM) adjusting for lack of independence at site and at practitioner level. Mean crying time will be entered as the dependent variable and group allocation as the explanatory variable. Results will be reported as between-group differences in average crying time in hours with 95% confidence intervals. P-values will provide the probability of this difference being null using Wald Chi2 test. If clustering effects cannot be identified (p-value>0.05), further analysis (i.e. sensitivity analysis, adjusted analysis, etc.) will use simple logistic regression without accounting for lack of independence. All analysis will be intention-to-treat (ITT) except for a secondary per protocol analysis on the primary outcome. All P values will be two sided, and the significance level set at 5%. All statistical analysis are to be done using StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.
Inclusion- / Exclusion Criteria	Excessive crying from infants can cause distress and lack of sleep in parents. Parents therefore seek solutions to reduce their infant's crying time. Such treatments are already common in UK, Australia and Switzerland without clear indication on its true benefit. Unsettled crying usually does not affect infants over 6 months of age. To evaluate the true benefit of osteopathic manual care, it is therefore necessary to involve infants. The trial will include infants (from age 1 week to under 10 weeks) who are healthy and thriving but are excessively crying, distressed or unsettled and or fussing and difficult to console. Excessive crying is defined as crying for more than 3 hours per day, more than 3 days per week for more than 1 week and is based on the Rome IV criteria used in the postnatal clinical classification of infants with difficulties settling, distress and excessive crying. Infants will be excluded if they: • have active co-morbidities that require medical attention or treatment prior to enrolment, • have already received osteopathic treatment, • have no tension in their bodies as palpated by the osteopath, • have neither parent who can understand and read German, French or English.
Number of Participants with Rationale	The data collected on crying time and standard deviations (SD) during the pilot phase (n=13, one diary was completed incorrectly) was consistent with observations made by Wolke et al. (2017). We estimated the average daily crying time over the two-week follow-up period to be 120 minutes with a SD of 46 minutes. To detect a minimum of 30 minutes additional reduction in crying time between the intervention and control groups, with 90% power and a two-sided 5% significance level, we would need 48 infants in each arm of the trial. If we allow for a 15% drop out rate, we will need to randomise 112 infants or 56 in each arm. Given there are three recruiting sites (UK, Australia, Switzerland), each site is to recruit 40 participants.
Study Intervention	Usual osteopathic care with osteopathic manual therapy treatment involving light touch for 10–20 minutes from one to four times over two weeks. Touch is directed at specific areas of the baby's body as deemed appropriate by the osteopath with the intent of bringing change to tissue function or fluid dynamics. Best practice advice will be drawn from the national UK guidance (NICE 2017, https://cks.nice.org.uk/colic-infantile)
Control Intervention	Usual osteopathic care including advice with non-specific generic light touch attention control on cranium, thorax, abdomen and sacral area in any order without any attempt by the osteopath to move or adjust soft tissues or modify fluid mechanisms. During touch, osteopaths undergo a cognitive task to divert attention from touch and avoid conscient

	interactions. Overall consultation duration is of 30-45 minutes, duration of targeted tension release is of 10-20 minutes, 1-4 times over two weeks.
Study procedures	**Recruitment**: Thirty UK, Australian and Swiss osteopaths will recruit participants in their own clinics. In Switzerland, at least 10 osteopaths are to be recruited. When a parent with a crying, distressed and unsettled baby calls the clinic to book an appointment, the osteopath, or their receptionist, will determine whether the baby fits the inclusion criteria, inform the parent about the study, and send them an invitation letter, the participant information leaflet and a consent form. All those interested in the study will be asked to record the number of minutes their baby cries in the 24 hours preceding their booked appointment. When the interested parents turn up for their baby's consultation they will be given the chance to ask questions about the study and asked if they want to participate. After providing their informed consent, parents will have their baby examined and screened to check overall health. If the baby is healthy, they will formally be enrolled in the trial and receive a unique identification study number (ID) and the parent will be asked to complete the baseline questionnaire online on a dedicated GCP and Data protection act compatible eCRF based in the Netherlands (CastorEDC) using the baby's unique ID. **Randomisation, allocation and blinding**: Block randomization is used to generate the randomization list to allocate patients to either the study or control interventions. Infants will be allocated to their group after baseline values are collected using the online data entry and patient management system (CastorEDC). There will be a standardised communication protocol between the osteopath and the parent during both the study and control intervention. The parents will therefore be 'blinded'. The parents will NOT be informed which treatment arm their infant has been assigned to, but they will be aware that the infant is receiving either the targeted or generic tension release. The parent will be present throughout the treatment and free to observe the delivery of the intervention. For the analysis the statistician will be blinded to the coding of each group. **Data collection**: Prior to the first treatment parents will complete a baseline questionnaire, a parenting confidence questionnaire, and a 24 hour crying diary. Parents will be required to complete an online crying diary every day for 14 days and record the dates and time of all treatments given. All participating parents will receive a questionnaire for follow-up information at 14 days, containing the parenting confidence questionnaire, a global impression of improvement question and a parent satisfaction questionnaire (please see section on data collection and outcomes). 14 days after randomisation (the first consultation), after completion of all questionnaires, parent can be informed in which treatment arm their infant was allocated to.
Study Duration and Schedule	*Overall project* First-Participant-In planned for February 2020 Last-Participant-Out planned for September 2021 *Switzerland* First-Participant-In planned for February 2021 Last-Participant-Out planned for September 2021
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Data privacy	All data will be captured and stored electronically, with the exception of the trial signed consent forms which are to be kept by osteopathic practitioners in their patient's records. The software (CastorEDC https://castoredc.com) provides facilities for electronic case report forms, survey questionnaire data capture and participant case history tracking information. Anonymity of the participants is ensured through the allocation of a unique study identifier. Confidentiality and blinding is ensured by access controls set by the study data manager. All data throughout the trial period is stored on the secure and backed up CastorEDC servers which complies with current EU and UK legislation and standards. All study material, including the final anonymised data set, will be archived and stored in a university repository for 25 years.
Ethical consideration	In Switzerland, over 40% of infant attend an osteopath during their first year of live. Unsettled crying is one of the most frequent reasons and amounts to an overall estimated yearly cost of about CHF 2'000'000. Given the global investments already accorded for osteopathic care, it seems important to collect evidence on its benefits. The safety of manual therapy care in infants has been the subject of review (Carnes et al 2016, Dobson et al 2008). As exposed in the previous paragraph, the reported incidence and prevalence of moderate and serious adverse events is very low with this form of gentle light touch therapy. Manipulation using manual thrust techniques are contra-indicated in this patient population and none will be used in this study. This study is expected to be a very low risk of harm in both arms of the trial especially as the treatment is very gentle and the condition is usually self-limiting and resolving. This study includes vulnerable participants. Including young infants is justified by the fact unsettled crying is specific to this age group and older children or adults are not affected. Consent from infants is impossible to obtain given their young age (≥70 days). A parent with legal authority will provide consent for their participation and their child's participation. All recruiting osteopaths (co-investigators) will undergo a two-day training course prior to participating in the trial that will cover recruitment, initial and ongoing consent and the law pertaining to consenting children via a parent, parents and good clinical practice in research.
GCP Statement	This study will be conducted in compliance with the leading UK protocol (IRAS_ID268925), the Swiss protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

Infants who excessively cry and are perceived as unduly distressed and unsettled may be otherwise healthy and thriving. However, these symptoms can have a marked impact on family life. Around 1 in 6 families are affected by excessive infant crying (Hiscock & Jordan, 2004). It is associated with maternal issues such as depression, anxiety and loss of parenting confidence (Johnson et al., 2015; Kurth et al., 2010). The peak age for crying in infants, at week six, is the same as the peak age for severe infant injury or death as a result of abuse (Berkowitz, 2017; Kato, 2016). Health care resource use by parents is higher in an infant's first 6 months of life, indicating a greater need for support during this period (Johnson et al., 2015). One of the major reasons for this increase includes unsettled infant behaviour and problems with sleeping and feeding (Morris et al., 2001).

While this behaviour is relatively common, there is a lack of consensus about its nature and cause which is compounded by limited research regarding the effectiveness of treatments currently used to manage the condition (Sung, 2018). Excessive crying, undue distress and/or unsettled behaviour are often grouped together under the heading 'colic'. Colic is usually self-limiting, however the UK National Institute for Health and Care Excellence (NICE) recommend reassurance and behavioural routines to help parents during this difficult period. Many parents seek alternative care such as osteopathy for their 'colicky' infants. In the UK, we estimate that the number of infants seen by osteopaths is around 61,000 per annum (C. A. Fawkes et al., 2014) which is approximately 1 in 11 or 9% of all infants born in the UK each year. There were 679,106 infants born in the UK in 2017 (Office of National Statistics UK). In Switzerland, where the density of osteopaths is the double than in the UK (12.9/100'000 residents versus 6.0), 10.3% of patients receiving osteopathic care are infants (Vaucher et al., 2018). This means that two infants out of five born in 2015 were seen by an osteopath in Switzerland.

One of the main reasons for parents seeking care for their infant is unsettled crying. Osteopathic treatment for 'colicky' infants commonly involves gentle touch and movement (Parnell Prevost et al., 2019). The intention is to relieve soft tissue tension in the infant's body, improve range of motion and function and promote better feeding and/or gut motility (Jäkel & von Hauenschild, 2012). Treatment includes gentle application of light tactile pressure to areas that are perceived to demonstrate palpably increased soft tissue tone. The osteopath maintains manual light pressure with the infant's body until the tension is felt to decrease and may also use gentle techniques to encourage movement in areas where movement is restricted (Jäkel & von Hauenschild, 2012).

There is little evidence to support the mechanism of action underpinning this approach with the rationale for treatment theoretically driven. Proposed physiological explanations include altered parasympathetic activity resulting from compression of the vagus nerve (Cowie, 2013; Lim, 2006) and/or cranial bone movement dysfunction (Kotzampaltiris et al., 2009), both attributed to birth trauma, with neither having been verified experimentally. Leuchter et al. (2013) postulated that infants with colicky crying were less able to regulate their responses to everyday stimuli. This led to the hypothesis that osteopathic affective touch may be able to modulate stimuli produced within the gut and other internal organs (interoceptive stimuli) in a direction that reduced symptoms such as crying and distress (Francesco Cerritelli et al., 2017; D'Alessandro et al., 2016).

Regardless of the physiological rationale or explanation for this approach, there is limited, low to moderate quality evidence to show that osteopathic and chiropractic care can help to reduce

crying time in infants (Carnes et al., 2018; Dobson et al., 2012; Parnell Prevost et al., 2019). There is evidence to show that this type of gentle light touch therapy has a low risk of harm (Carnes, Mars, et al., 2010) and that adverse events reported were transient and low to moderate in severity (Parnell Prevost et al., 2019). However, more scientifically robust definitive trials on the topic are needed to clarify the situation.

It is recognise that parents/carers are often in crisis when they seek support and care for their 'colicky' infants and that they expect the outcome of that care to have an almost immediate effect. This study has therefore been designed to look at only the short-term impact of care. The reasons for this are two-fold: i) to limit the stress on the parent/carer (the peak time for crying is during the infants first six to eight weeks of age), and ii) because normally the symptoms of excessive crying, unsettledness and distress are self-limiting and start resolving around nine to 12 weeks of age (Wolke et al., 2017). Parents/carers in both groups will receive recommended advice and information drawn from national clinical guidelines (NICE 2017). The inclusion of a 'non-touch' control group was not possible due to the inability to blind the parents/carers of infants in such a group.

The aim of this study is therefore to evaluate the effectiveness of osteopathic manual therapy care for excessively crying, unsettled and distressed infants under 10 weeks old. The study will compare the effect of osteopathic specific light touch manual therapy care delivered with therapeutic intent with a non-specific light touch manual intervention. The trial will provide data regarding the belief of both osteopaths and parents/carers, that the 'therapeutic intent' associated with the directed osteopathic light touch is the active element in delivering benefits.

3 STUDY OBJECTIVES AND DESIGN

3.1 Objectives

Our *principle objective* is to measure the superiority of osteopathic light touch over non-specific light touch in reducing average daily crying time over two weeks in unsettled crying infants measured by a daily diary completed by infant's parents.

Secondary objectives are to measure effects on confidence in parenting skill, global impression of improvement, parent satisfaction and experience, and cost of treatment.

3.2 Primary and secondary endpoints

The primary endpoint

Reduction of average crying time over two weeks between the active treatment compared to the control. The crying diary used in this trial has been validated against 24-hour recordings of infant vocalisations in a general population sample over a 7-day period (Barr et al., 1988). Correlation between parent/carer noted crying and recorded negative vocalisation was r=+0.90 (p=0.001). In the population sample of 409 eligible participants, 91% of the diaries received were completed sufficiently for analysis. The set minimal clinical important difference is of 30 minutes crying reduction per day.

Secondary endpoints

Parenting confidence is assessed using the Karitane Parenting Confidence Scale (Črnčec et al., 2008). This 15-item questionnaire has a four level Likert scales (no, hardly ever, =0, no, not very often=1, yes, some of the time=2, yes, most of the time=3) with higher scores indicating better parenting confidence (range from 0 to 45). The instrument showed good internal consistency (Cronbach's alpha=0.81), test-retest reliability (r=0.88) and high transcultural validity in Portuguese (Pereira et al., 2018), Danish (Pontoppidan et al., 2019), Japanese (Usui et al., 2020) and Nepali (Shrestha et al., 2016). Reliability change index identified a change of six points as the minimal clinical important difference.

Global change, satisfaction and experience questions are those used and tested for reliability and validity in the National Council for Osteopathic Research (NCOR) Patient Reported Outcome Measures (PROM) application and online data capture system (Fawkes et al., 2010; Froud et al., 2018). Global impression of improvement is assessed using the single question “Overall, how would you rate your child’s change in symptoms since they started having treatment?” with a seven level Likert scale (Completely recovered=3, Much improved=2, Slightly improved=1, No change=0, Slightly worse=-1, Much worse=-2, Vastly worse=-3). Parent satisfaction is measured asking parents a single question “Overall how satisfied were you with the care your baby received at the practice?” with a five step Likert scale (Very satisfied=2, Fairly satisfied=1, Neither satisfied nor dissatisfied=0, Fairly dissatisfied=-1, Very dissatisfied=-2). Parent’s experience was measured using a single question “Overall how would you rate your experience at the practice?” on a five step Likert scale (Very good=2, Fairly good=1, Neither good nor poor=0, Fairly poor=-1, Very poor=-2).

Direct cost is to be estimated from the number and duration of sessions at the usual fare.

All questions have been translated to German and French and obtained face validity by bilingual practitioners.

Safety endpoint are the rate of light, moderate and sever adverse events reported by parents during follow-up and classified according to the taxonomy specifically developed for manual therapy (Carnes, Mullinger, et al., 2010). Serious adverse events are also to be described in detail for each group, but their number is expected to be too low for any statistical comparability between groups.

Baseline data that could influence results are initial evaluated daily crying time, age and parental confidence.

3.3 Study design

This study is part of a running multicenter, international, UK led pragmatic single-blinded two-arm parallel randomised controlled trial. It is designed to compare the difference between best usual advice with the addition of osteopathic manual therapy and best usual advice with a non-specific attention control in infants (<10 weeks old) who excessively cry, are distressed and unsettled (the infants in the control arm will receive a ‘light touch non-specific’ intervention for the same amount of time as the infants being treated in the intervention arm).

The control arm will involve a case history, a health screening (and hence reassurance that the infant is otherwise well and not requiring onward referral) and best practice advice (based on UK

NHS guidance), and a light non-specific touch attention equivalent design which is not intended to be an active physical manual treatment. There are studies comparing light touch massage that show a small difference in beneficial outcomes for behavioural states (Field et al., 2006; Vickers et al., 2004) and other studies that show there are contextual beneficial elements of care involving touch (Meltzoff et al., 2018; van den Hoogen et al., 2017). This means all infants and parents will receive best practice advice and the equivalent benefits of touch.

For manual therapy, blinding is difficult to achieve for those providing care (Cerritelli et al., 2016). Therefore, the study focuses on assuring blinding for parents, infants, operators measuring baseline values and follow-up outcomes, and the statistician.

All infants will receive a standard health screen and parents will be able to discuss issues and be given advice. Ethically, this accommodates the supportive needs of parents when dealing with excessively crying infants, by providing psychological and social support, which is included in all the consultations with advice given by osteopaths.

3.4. Study intervention

The intervention under investigation is osteopathic manual therapy treatment for unsettled crying in infants. Treatment are given for approximately 10–20 minutes up to four times over two weeks. The treatment involves light osteopathic touch using techniques such as articulation, tension release (to ligaments, articular strains, fontanelles/cranial sutures), counter-strain/facilitated positional release, indirect functional techniques, myofascial release, soft tissue massage and/or stretch and visceral mouvement. Touch is directed at specific areas of the baby's body as deemed appropriate by the osteopath as done in usual paediatric osteopathic care. The intervention arm relies on light touch osteopathic manipulative treatment (OMT) whereas the control group also benefits from an active treatment which consists of usual osteopathic care with a non-specific light touch contact.

Osteopathic Manipulative Treatment (OMT) arm

The infants randomised to the specific light touch intervention arm will receive osteopathic usual care. Each infant in this arm will be given osteopathic manual therapy treatment as appropriate for approximately 10-20 minutes. Predetermined protocolised general information will be communicated with the parent/carer during the treatment. This arm is called the "*Targeted Tension Release arm*" (TTR). It involves light osteopathic touch directed at specific areas of the baby's body and is designed to reduce tension in the soft tissues and promote circulation. This is considered usual osteopathic care. The TTR can be applied to any of the following areas: cranium, neck, face, shoulders, thorax, abdomen and sacral area in any order as deemed appropriate by the osteopath. Administering TTR involves gentle touch that includes movement of the relevant soft tissues and fluids using techniques such as articulation, tension release (to ligaments, articular strains, fontanelles /cranial sutures), counter-strain/facilitated positional release, indirect functional techniques, myofascial release, soft tissue massage and/or stretch and visceral movement.

Techniques excluded in this trial are high or low velocity thrust manoeuvres and muscle energy techniques.

Control arm

Infants randomised to this group will receive non-specific light touch consisting of a non-specific generic light touch attention control intervention for approximately 10-20 minutes. Predetermined protocolised general information will be communicated with the parent/carer during the treatment. This is called the "*Generic Tension Release arm*" or GTR group. It involves non-targeted light touch on the baby's body.

The GTR can be applied to any of the following areas: cranium, thorax, abdomen and sacral area in any order without any attempt by the osteopath to move or adjust soft tissues or fluid mechanisms. It will be delivered without any therapeutic intent. To prevent any treatment intent, the osteopath will be required to perform a cognitive task while holding the infant. For example, the osteopath will be required to count backwards in 6s, 7s or 8s from 200 (Cerritelli et al., 2017) or to recite animal or vegetable names starting with specific letters of the alphabet (in their minds only).

The treatment components in both arms of the trial

All participants will receive care in the form of a consultation consisting of a health screening examination and best practice advice. All care given will be at no charge. The consultation will consist of five phases:

I. A history of the pregnancy, birth and infant.
II. Standardised health and osteopathic screening of the infant.
III. Discussion of findings of the examination followed by parental/carer consent for light touch treatment and to be in the trial.
IV. The randomised intervention.
V. Best practice advice on feeding, sleeping, and manual handling of the baby will be given to all parents/carers verbally and in the form of an information leaflet or an online URL, depending on the preference of the parent/carer. Best practice advice and guidance will be based on NICE Guidance 2017.

All participants will be scheduled to receive up to four intervention sessions over a two-week period as deemed appropriate by the treating osteopath and agreed to by the parent/carer. The number of consultations is defined by osteopaths as they would do during usual care. The determinants they are believed to rely on are, severity of the condition, level of parental distress, availability of parents, availability of practitioner. The UK pilot study showed that the number of consultations were similar between the targeted and generic groups. A standardised patient health screening, case history, and treatment tracking form will be used by all participating osteopaths for all trial participants. This will ensure that the consultation content is recorded consistently. The standard health screen (conducted by the osteopath) will assess the infant's height, weight, temperature, respiration, pulse, colour, muscle tone, symmetry and movement. All parents will be informed of the findings from their infant's health screening. If the examining osteopath is of the opinion that the infant has an underlying medical condition that requires medical attention, they will not enrol the infant in the trial and will refer the infant and parent/carer to their GP or in the case of an emergency, to the Accident & Emergency department of the nearest hospital. Such circumstances include the presence of fever, sustained rash under pressure, infection or the presence of any severe mental health issues on the part of the parent/carer. Assuming that the osteopath considers the infant to be suitable for the trial, they will

then inform the parent/carer that the infant might have some underlying tension in their soft tissues and restricted movement/s which might explain some of the distress that the infant is displaying. The osteopath will then explain to the parent/carer that they would like to gently touch the infant with the aim of reducing tissue tension.

This study will explore whether targeted specific osteopathic light touch is superior to non-specific light touch. Non-manual contextual components of the intervention will be delivered with therapeutic intent in both groups. The potential placebo and nocebo elements are present in both groups. Parents will not be asked to desist from using any other care strategy during the trial period.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

One hundred and twenty infants, 40 from Switzerland, are to be included in a 1:1 ratio between OMT and control group. One parent and their infant are to be enrolled. The parent is the person who has legal authority over the child and takes care of the child most of the time. In case of equally shared parenthood, parents choose one person who will be responsible of reporting crying time and answering questionnaires.

Inclusion criteria for parents

- Legal representative of an infant responding to inclusion criteria.
- Age of 18 years or above.
- Mastery of French, German or English to understand the information and consent form, and answer questionnaires.
- Able to give informed consent as documented by signature.

Inclusion criteria for infants

- Infants aged from 1 to 10 weeks (8 to 70 days). This time-frame is important as unsettled crying usually resolves spontaneously after 12 weeks of age and the treatment period is to last two weeks.
- Infants are healthy and thriving.
- Excessively crying, distressed or unsettled for more than 3 hours per day, more than 3 days per week for 1 week or more. This definition is adapted from the Rome IV criteria used in the postnatal clinical classification of infants with difficulties settling, distress and excessive crying

Exclusion criteria for infants

- Active co-morbidities that require medical attention or treatment. This is to limit serious confounders and ensure that the infants recruited are healthy and thriving and that osteopathic care is not inappropriate.

- Priorly or under treatment with an osteopath for similar reasons.
- Already in a clinical trial.

Vulnerable population

This study includes vulnerable participants. Including young infants is justified by the fact unsettled crying is specific to this age group and older children or adults are not affected. Consent from infants is impossible to obtain given their young age (≤70 days). Both in the UK and in Switzerland, parents often seek complementary/integrated care during the period after they are discharged by their gynaecologist and before their child is managed by a paediatrician. Apparently, there is a high demand for support during this period. Parents are already seeking care for which no evidence of benefit exists.

A parent with legal authority will provide consent for their participation and their child's participation. All recruiting osteopaths (co-investigators) will undergo a two-day training course prior to participating in the trial that will cover recruitment, initial and ongoing consent and the law pertaining to consenting children via a parent, parents and good clinical practice in research. Parents will be provided with written information, access to the study team and their osteopath for questions and be given the consent form in advance to look at and discuss with family and friends, should they wish, before taking a decision about enrolling their infant in the trial. Verbal consent will be sought prior to the consultation and written consent after the initial examination of the infant to confirm eligibility of infants health prior to written consent and enrollment. Parents are informed they can withdraw their consent at any time without impeding on usual care. Further details on the consent procedure is detailed in the next section.

4.2 Recruitment, screening and informed consent procedure

Recruiting usual care osteopathic care providers

Clinicians are recruited by local investigators using existing networks in osteopathic paediatric care. In Switzerland, patients are recruited under the local investigator's supervision by NAREG registred osteopaths working in their own private practices (co-investigators). Osteopaths belonging to the OsteoHub networks are invited to contribute to the study (N=230). To be eligible, osteopaths have to have at least 1 year of post-graduate working practice, follow at least one infant per week, and master English well enough to understand written documents and follow the two-day training organised within the study.

The training program consists of training in the trial procedures including the standardised consultation, infant health screening, recording of findings, manual techniques to be used, protocol for the control intervention group, advice to give to parents/carers and procedures for recording adverse events and Good Clinical Practice in research. In addition, the osteopaths will receive safeguarding of children training so that they can identify children who may be at risk and be aware of the procedures and protocols to deal with such children. Dawn Carnes and Paul Vaucher are in charge of delivering the training to the Swiss osteopaths. Given the covid-19 situation, it takes place online using Teams and is organized by the HEdS-FR. The training also provides clear instructions and material to execute the protocol. Osteopaths are also required to practice procedures before starting to recruit.

Participation by an osteopath may be used to contribute to continuing professional development requirements undertaken as part of their professional standards regulatory board's expectations in their respective jurisdiction. In Switzerland, as a compensation, osteopaths receive CHF 300.- for the first pair of participants they recruit, and 200.- for each additional pair.

Patient recruitment

Participants are recruited at four different sites, two in the UK, one in Australia and one in Switzerland. In Switzerland, infants and their parents/carers will be recruited directly via osteopathic clinics and private practices (secondary sites) or indirectly through posters in private osteopathic practices or referrals from midwives, paediatricians, pre-natal and ante-natal groups, who may hear about the trial through word of mouth, social media and/or promotional posters.

Most patients are identified by the secretary services who books appointments. Osteopaths inform their secretary service to systematically offer the opportunity to enter the study for any parent taking an appointment for their child who presents colic. Some osteopaths work with midwives, paediatricians or clinics who will expose and/or deliver the recruitment form to parents with children who present colic.

When a parent/carer with a crying, distressed and unsettled baby calls the clinic to book an appointment, the osteopath (or the receptionist) will ask the parent/carer if their baby is between 1 and 10 weeks old, cries for more than three hours per day for three days or more over at least one week (Zeevenhooven et al 2017) and is difficult to console. Those interested in participating in the study will be asked to record the number of minutes their baby cries in the 24 hours preceding their booked appointment. When an interested parent/carer attends their scheduled consultation, they will be given the chance to ask questions about the study and advise if they want to participate. The choice of the osteopath by the parents precedes the sending of the study documentation, unless the parents come forward after reading a recruitment announcement.

Screening

Screening process does not include investigations or questions different than those used in usual care. Those participants who respond to advertisements (i.e. self-referred) will be asked about their infant's crying and health by a member of the study team or the recruiting osteopath to ensure that they are eligible to be included in the trial. If the baby meets these inclusion criteria, the osteopath (or receptionist) will inform the parent/carer about the study and ask if they are interested in receiving the invitation letter, participant information leaflet and consent form. The osteopath will record the date of the invitation, outcome and, where appropriate and if possible, the reasons for declining (anonymously).

The infant will be enrolled in the trial if they meet the inclusion criteria and are suitable and given a unique identification study number (ID). The parent/carer will then be asked to complete the baseline questionnaire electronically (either using their mobile phone, clinic online facility or paper version if there is no online facility) using the baby's unique ID. This step should take approximately five minutes.

Refusals

Those who express that they are not interested in participating in the trial will go on to be booked an appointment independent of the trial as per standard clinic procedures. Those who decline will be asked, where applicable, for their reason for declining and this will be recorded in a recruitment rate log. However, parents are under no obligation to justify their refusal to participate in the study.

To determine response rates, the recruiting osteopaths, or research team member will record the number and date of those interested, eligible and invited into the study but who declined including, if possible, the reason for that decision.

Informed consent process

The co-investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her health records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Participating parents/carers will receive an invitation letter, participant information leaflet, consent form and the crying diary when they express an interest in being part of the study. This information will be sent a minimum of 24 hours prior to their consultation to help them make an informed decision about participating.

They will also have an opportunity to ask any questions or concerns about the study, with either the recruiting osteopath or a member of the study team at any point before the initial consultation begins. Consent will only be requested once a parent/carer is satisfied they have all the information they require to make an informed decision. The recruiting osteopath will counter-sign the consent form and return a copy to the study team.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure.

The consent form will be signed and dated by the co-investigator or his designee at the same time as the participant sign. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records. The informed consent process is documented in the patient file and any discrepancy to the process described in the protocol must be explained.

Compensation

Patients, parents/carers will not be compensated for their participation. They will however not be charged for the care provided by the osteopath during the follow-up period of the trial.

4.3 Study procedures

Pilot study

A pilot feasibility study was conducted in the UK to test the feasibility of a number of the trial's processes and procedures. These included: an estimation of recruitment rates, whether the osteopaths could be trained to deliver both the intervention and control arm of the trial as per protocol, parent/carer blinding and compliance, and accuracy rates for the electronic online data collection and crying diaries. Fourteen infants and parents were recruited, and 31 osteopaths were trained. Results from the pilot study showed that one in five parents with excessively crying infants who were approached for the study decided to participate in the trial. Only 25% of the osteopaths who underwent training in the trial protocol went on to recruit and treat infants into the trial. This prompted a change in recruitment strategy from general recruitment to the establishment of dedicated CUTIES trial clinics with only trial osteopaths and targeted advertising for these clinics. Compliance with electronic data capture was successful with parents preferring this system over paper-based collection. We asked parents about their group allocation at follow up and this showed that parental blinding was successful. We used the crying diaries to calculate the mean daily crying time and standard deviation between groups to determine sample size for the current protocol.

Randomisation procedure

Randomisation will be 1:1. Block randomisation will be used with a variable block size of 4 and 6 generated in real time online. Sequence generation is assured automatically by the web-based platform used for data management (CastorEDC – https://uk.castoredc.com). Allocation is provided by the same platform after the treating osteopath has confirmed consent, ensured the baby is healthy and a completed baseline questionnaire has been submitted.

Allocation is then registered within the system and is made available to the treating osteopath using the web-based platform.

Blinding

The chief investigator, the principle investigator, parents/carers, infants and statistician are blinded to allocation. Osteopathic practitioners (co-investigators), who provide care, and data manager, who will have no contact with participants, will not be blinded.

Parents/carers will NOT be informed which treatment arm their infant has been allocated to but they will be aware that the infant is receiving either the OMT or control intervention.

There will be a standardised communication protocol between the osteopath and the parent/carer during both the OMT and control intervention sessions. It will be delivered at pre-set intervals during each session and include comments such as "your baby is doing very well", "I have nearly finished checking and treating your baby", "a few more minutes" and "we have now finished the treatment". Each intervention session will last between 10 and 20 minutes. The osteopaths will be permitted to make soothing and/or playing noises with the infant during these sessions.

Should the parent wish to ask questions about the hands-on touch, the osteopath can talk in general terms about the explanatory theories associated with gentle light touch care but not about the touch they are giving, as the parent has consented to be blinded to this.

A parent/carer will be present throughout the treatment session and free to observe the delivery of intervention. However, parents/carers will remain 'blinded' throughout the active phase of the trial so that outcomes are not biased a priori by parent/carer expectations. Naming both intervention arms with equal suggestibility with respect to treatment supports this intention. To assess blinding, at the two-week follow-up, each parent/carer will be asked which group they believe their infant was allocated to, we will then compare these guesses between both groups using a Fischer's exact test.

Once the participant has completed and returned their follow-up questionnaire and their crying diary they can be informed about their infant's allocation. If they do not complete their follow-up information, their allocation can be divulged at 21 days or after, post randomisation. Unblinding of the parent will occur in the case of serious adverse events and or complaint and withdrawal from the trial.

To maintain blinding during statistical analyses, the statistician will also be blinded to group identity.

Data collection and management

In Switzerland, patients are to be recruited by co-investigators during a six month period. Prior to the first treatment, a parent/carer will complete a baseline questionnaire, a parenting confidence questionnaire, and a 24-hour crying diary. These questionnaires will be made available using CastorEDC, a Dutch based secure data management system for collecting research related data. Osteopaths will be encouraged to build rapport with each parent/carer and offer as much counsel and support as necessary. The interval between treatments will be determined by the treating osteopath in consultation with the parent(s)/carer(s) of the infant. Parents/carers will be required to complete an online crying diary every day for 14 days as well as recording the dates and times of all intervention sessions attended.

All participating parents/carers will receive an electronic follow-up questionnaire at 14 days post initial intervention. It contains a second parenting confidence questionnaire, a global impression of improvement questionnaire and a parent satisfaction questionnaire.

Parents will receive a reminder to complete their follow-up questionnaire and diary on day 18 post randomisation if no returns are received.

Table 1 Data collection time points

Baseline	Over 14 days	14 days post randomisation
• Last 24 hours crying time • Age of mother • Age of infant (weeks and days) • Gestational age (weeks and days) • Gender of infant • Birth weight • Current weight • Number of other siblings • Parent/carer, confidence in parenting * • Parent/carer status (alone or co-parenting) • Number of other children	• Number of minutes of crying time per 24 hours over 14 days • Adverse events: All serious adverse events will be reported to the study team immediately by either the treating clinician osteopath or by the parents/carers directly to the study team either by telephone or by email, depending on the nature of the event.	• Parent confidence in parenting * • Parent satisfaction and experience with osteopathic treatment • Parent rated: Global change score • Other co-treatments used (tick list question) • Information about unexpected and or unwanted outcomes • Group allocation belief

*(Crncec *et al* 2008, Karitane Parents' Confidence Questionnaire)

4.4 Withdrawal and discontinuation

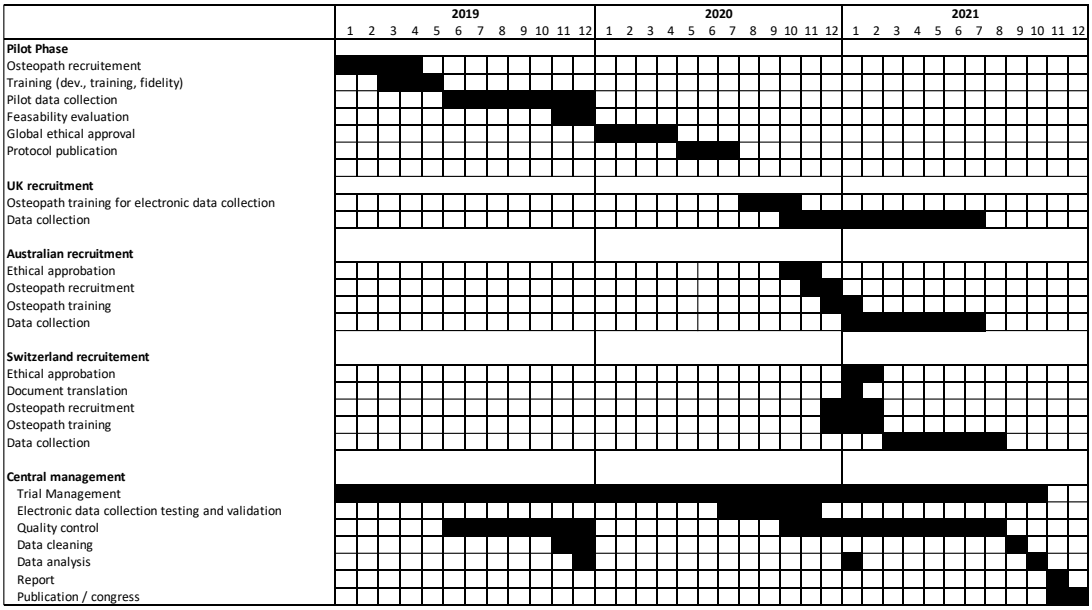
Participant are withdrawn from the study if:

- Parent withdraws informed consent.
- Other legal representative (parent) is in disagreement with participation.
- Major protocol deviation occurs in disrespect of inclusion criteria.

Co-investigators are to inform principle and chief investigator of protocol deviation within 24h after they are acknowledged. Withdrawal are to be noted in patient records. Contact details can be kept by co-investigators that follow patients but are to be removed from all other documents (principle and chief investigator list).

4.5 Planned schedule

The Swiss trial is meant to run from February 2021 to at latest September 2021.



5 STATISTICS AND METHODOLOGY

5.1 Statistical analysis plan and sample size calculation

The analysis of the data will be carried out on the entire data collected by the international consortium. The Swiss data is therefore embedded in the overall analysis.

Sample size estimation

The data collected on crying time and standard deviations (SD) during the pilot phase (n=13, one diary was completed incorrectly) was consistent with observations made by (Wolke et al., 2017). We estimated the average daily crying time over the two-week follow-up period to be 120 minutes with a SD of 46 minutes. To detect a minimum of 30 minutes additional reduction in crying time between the intervention and control groups, with 90% power and a two-sided 5% significance

level, we would need 48 infants in each arm of the trial. If we allow for a 15% drop-out rate, we would need to randomise 112 infants or 56 in each arm. Each country is expected to enrol 40 participants or four patients from 10 secondary sites.

Descriptive statistics

Descriptive statistics will be used to summarise the characteristics of participants in each group in the trial. This will include baseline values, treatment schedules, compliance and follow-up. We will show number and percentage or mean and standard deviation for categorical and normally distributed continuous variables respectively. For data severely deviating from a normal distribution, we will present median and interquartile ranges. Probability of observed between groups difference will be calculated by using Fisher's exact, Chi2 test, Mann Whitney U test and, or Student's t-test as appropriate.

For crying time, the Bartlett's periodogram-based test for white noise will be used to test the assumption of constant mean and variance for each individual. Analysis of graphical representation will define which transformation would best model trend over time. If a clear change of effects happens abruptly over time, the data will be additionally analysed over separate time periods, by default separating the first week from the second. If such a trend exists, secondary analysis will also compare differences for indicators of this trend between groups.

Primary outcome analysis

We will analyse the primary outcome of mean crying time using a multilevel mixed-effects generalised linear model (GLM) adjusting for lack of independence at site and at practitioner level. Mean crying time will be entered as the dependent variable and group allocation as the explanatory variable. The hierarchical multilevel datasets are assumed to have normally distributed random effects. Likelihood ratio test will be used to test for clustering effects. Results will be reported as between-group differences in average crying time in hours with 95% confidence intervals. P-values will provide the probability of this difference being null using Wald Chi2 test. If clustering effects cannot be identified (p-value>0.05), further analysis (i.e. sensitivity analysis, adjusted analysis, etc.) will use simple logistic regression without accounting for lack of independence.

Secondary outcomes analysis

The same method will be used to test secondary outcomes. Categorical response variables using Likert scales (i.e. global change, parent satisfaction) will be analysed using a proportional odds model. Between group changes in parenting confidence score will compare changes from baseline by entering baseline score as an explanatory variable in the GLM model.

Proportion of participants who reported at least one adverse event will be compared between groups using a Fisher exact test. The same approach will be used to compare unexpected reactions (distress, crying, unsettled, vomiting, difficulties feeding, difficulties sleeping, other).

Exploratory analysis

We will:

- Explore explanatory variables at a practitioner level to model between osteopath heterogeneity if present.
- Describe eventual correlation between years of experience and treatment effects (*i.e.* analysis of trends and comparison for cut-off at 3 or less years versus more than 3).
- Investigate eventual association between post-graduate training and treatment outcomes (interaction term).
- Test whether adjunct treatments were similar between both groups to assess unequal treatment bias.

Sensitivity analyses

In a worse-case scenario in an intention to treat (ITT) analysis, we will replace those who are lost to follow-up and missing data for primary outcome with highest observed crying times values in the TTR group and lowest crying time values in the GTR group.

Attrition bias could occur if the number of consultations is unevenly distributed between groups. Therefore, secondary analysis will verify that results are not influenced by uneven distribution of number of consultations. This will be done using random-effects generalised least-square regression adjusting for lack of independence at practitioner level.

Complementary confirmatory analysis

- Separate analysis between 1st and 2nd week (stratified analysis underpowered).
- If baseline imbalance (p-value<0.10) is observed, a secondary analysis with adjustment for these variables will be run to confirm results.
- Per protocol analyses.

All analysis will be intention-to-treat (ITT) except for a secondary per protocol analysis on the primary outcome. All P values will be two sided, and the significance level set at 5%. All statistical analysis are to be done using StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. Statistical analysis is managed by Paul Vaucher who is responsible of preprograming the entire analysis prior to data collection, of justifying protocol deviation and obtaining approbation from the trial steering committee whilst still blinded from allocation, of running the analysis and delivering the statistical report.

Stopping rule

There are no statistical stopping rule. The trial will be stopped if another high-quality definitive research trial shows that this type of intervention is either highly effective, or is harmful and renders the continuation of this trial inappropriate. The Data Monitoring Committee (DMC) will review the data after 75 infants have been recruited and followed up, to determine progress. The trial will not proceed if more than half the parent participants do not complete their crying diaries, withdraw from the study or if the DMC considers that participants experience too many serious adverse events.

5.2 Handling of missing data and drop-outs

Missing data from diaries will be accepted if at least eight separate entries over two weeks are provided. The average daily crying time will then be provided by averaging the crying time over the available days. As missing data cannot be assumed to be missing at random, complete case analysis is to be done. A sensitivity analysis will then evaluate effects on results with the worst-case scenario (imputation of highest observed effect if in control and lowest if in OMT group).

Drop-outs from treatment are to be followed-up and questionnaires delivered as if treatment had continued (ITT approach). Data from participants who have dropped-out or could not be followed will be replaced by new subjects.

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

6.2 (Serious) Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial invervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible. Adverse events are to be classified using an agreed taxonomy for manual therapy drawn from a consensus study (Carnes et al. 2010).

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Chief-Investigator of the study (international investigator) by the Principle-Investigator (site investigator Switzerland).

Adverse event monitoring will be done by the treating osteopaths, scrutiny of the follow up questionnaires and contact with the study principal investigator (PI) who may receive complaints or concerns from parents/carers directly. An independent reporting mechanism to a person independent of the trial's study team also exists (details are provided on the participant information sheet). An adverse event report will be generated within 24 hours for any unwanted or unexpected incident, event or accident that is reported. In the case of serious adverse events such as death or unplanned hospital admission, an adverse event report will be generated immediately for both the local and the international sponsors.

In Switzerland, the Swiss Principal Investigator is responsible for reporting events to the local sponsor, the Chief investigator and the local Ethical Committee. If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the local Principal Investigator reports it to the Ethics Committee via BASEC within 15 days. Decisions regarding stopping the trial on all sites are to be made by the main sponsor following the UK ethical standards with the NHS (DMC and NHS ethical board).

Follow up of (Serious) Adverse Events

Principal investigators at a national level are to monitor evolution of conditions for participants terminating the study with SAEs. This is done in close collaboration with co-investigators. Patients or parents are contacted by phone or E-mail, depending their preferences, until resolution or stabilisation. This is to be done once a month for the first six months and once every three months afterwards.

Even in the absence of adverse events, After the 14 day period of the trial. The parent can make decisions about their child's onward osteopathic care should they deem it appropriate, this care would be delivered and priced as per normal clinic practice. All other care will continue as normal during the trial and after.

6.3 Safety reporting

For the Swiss part of the study, an annual safety report (ASR/DSUR) will be submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs). Given the study is not to last more than a year, a single report is planned for December 2021. This report will include information on SAE from all sites including those out of Switzerland.

The Swiss site is a secondary site. All SAE from the three national sites are reported to the Chief Investigator using ICH E2A standards as required by the NHS. SAE from other countries are therefore not reported using the ASR/DSUR.

6.4 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Central Ethics Committee for approval before implementation. Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29). A list of substantial changes is also available on www.swissethics.ch.

The Central Ethical Committee capable of approving changes is the London – Survey Research Ethics Committee linked to the NHS Health Research Authority. Local ethical Committees are to be informed of the approved changes.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the local and central Ethics Committee as soon as possible.

A list of all non-substantial amendments will be submitted in December 2021 to the competent EC together with the ASR.

6.7 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38). Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

6.8 Insurance

Sponsors and employees liability for harm to participants arising from design of the research

All protocol authors and members of the trial management team are either employees of established universities and hold employers insurance as part of their contract of employment (DC, PV, SV, PB, RE, SG). One member is a registered private practice osteopath who holds her own insurance (KC) and the lay member we have yet to recruit will be part of the university college of osteopathy patient and public involvement group who are also insured by the University College of Osteopathy.

All damage that could occur to Swiss participants are covered by by the School of Health Sciences Fribourg liability insurance by “La Bâloise” for this specific study (Police 2071361362).

Sponsors, employees and mandated clinicians employees liability for harm to participants arising from management and conduct of the research

The Swiss sponsor reserves its right to hold partners accountable for their own responsibilities.

- All recruiting osteopaths are required by law and as a condition of their registration to have indemnity and public liability insurance. For Switzerland, authorization of practice requires having a liability insurance covering up to CHF 5'000'000.-. Each co-investigator has their own insurance and provide details on their insurance policy to enrolled patients.
- National sponsor liability insurance covering all damage, loss or compensation due to an unexpected event linked to the study and related to patient management, local data management, and any other tasks under the site principle investigator's responsibility.
- Central sponsor liability insurance covering compensation due to data breach, loss of data, or any other event under the responsibility of the Main Central Trial Management.

International insurance
UK, University College of Osteopathy, Insurance with RSA, RTT2837162018

Switzerland national level insurance
CH, HES-SO | FR, Insurance with Bâloise, Police 2071361362

7 FURTHER ASPECTS

7.1 Overall ethical considerations

Ethical approval

- For the pilot phase, ethical appraisal and approval was granted by University College Osteopathy Ethics Committee (05.06.19) Ref: CUTIES trial.
- The main trial received ethical approval from the London-Surrey National Health Service Research Ethics Committee: IRAS # 268925 19/LO/1620 (09.11.19). This organisation is the Central Ethical Committee for the trial.
- The Australian arm of the trial received ethics approval from Southern Cross University Human Research Ethics Committee (HREC), approval number 2019/569.
- The Swiss arm of the trial received ethical approval from Swiss Ethics, approval number 2021-00099

Public and participant involvement

Parents of infants who are 'colicky' or who have been labelled with 'silent reflux' were consulted about the design of the study, particularly the interventions and blinding. All the participant facing material has undergone review by two women who have recently experienced birth and cared for a distressed infant. They reviewed the material and made some insightful comments and suggestions to improve the participant information leaflet, the recruitment poster and the trial questionnaires. A patient representative also sits on the trial management committee and the trial steering committee. Where possible, parents will be involved in the dissemination of the results of the trial by contributing to presentations.

Self-limiting condition in healthy infants

Some people may argue that as 'colic' is a self-limiting condition in most cases there is no point in treating these infants or indeed researching the topic. The reality is however that there are practitioners 'treating' infants with colic and there is a demand from parents for 'treatment' and or additional support. These practitioners in private practice will also charge for the care. Parents need robust information and evidence to be able to make informed decisions about the care of their infants.

Consent of infants

Parent participants will not be enrolled in the trial unless consent is informed and valid. All participants will be given a participant information leaflet and access to the study team and their osteopath should they have questions about their involvement. The infant will have a specific trial case record form to which the study team will seek consent to access, no request for access to other personal medical records of the infant or the parent will be sought.

Child protection

In terms of child protection, participating osteopaths will need to be registered osteopaths and therefore be considered to be able to treat children. The risks to the infants from the manual therapy treatment are low (Carnes et al., 2018; Carnes, Mars, et al., 2010), however the study team are aware that parents can have strong emotional reactions. We will therefore ensure that our training course for osteopaths includes distress management. Should any parent participant become unduly distressed they will be helped by the osteopath who will listen and support the parent until they are sufficiently able to leave the consultation room and care for their infant. However, we recognise that in some circumstances it may be necessary, and with the participant's agreement, to seek further help from a more suitable health care professional. Under no circumstances will an infant or parent be left unduly distressed. If the osteopath feels that the parent participant is a danger to themselves or others, they will seek permission to contact the parent participant's normal GP or take them to Emergency care. In terms of safeguarding each participating osteopath will be required to inform themselves of the 24/7 safeguarding procedures and contact numbers in their locality should they deem a child is at risk or if the parent is at risk of harming them-self or their child or children.

Safety

All interventions administered with therapeutic intent have some component potential to harm as the intent is to change something. This process of change can be considered from a biopsychosocial perspective. From a biological or physiological perspective the intervention and health screening is minimally invasive and gentle thereby reducing the risk of injury and creating an opportunity to identify any other conditions requiring referral to another health care professional. We are recruiting osteopaths who are experienced in treating infants and therefore we expect that they have made suitable modifications and arrangements in their clinical setting to accommodate treating infants. The minimum level of health and safety requirements will be addressed in the participating osteopath training courses, for example safeguarding, hygiene and cleanliness, use of toys to BSI UK and or EU standards and appropriate handling infants.

Psychological distress

Psychological distress is more probable at the parent level. Osteopaths participating in the study will be trained to observe the level of anxiety, stress and vulnerability of the parent and give appropriate best practice advice and action. In some unlikely cases, parent participants may be at risk of harming themselves or their infant. In this situation, in the first instance the osteopath will suggest the parent to seek further support for themselves (GP or appropriate family support or support group). At the next level should the parent be unsure about seeking help, the osteopath will offer, with the parent's permission to seek help on their behalf (GP or appropriate family support or support group). Should the patient refuse both these pathways and the osteopath is so concerned about the immediate safety of the parent or the infant, in Switzerland, they are to call the Cantonal Physician and explain the citation and ask whether they are authorised or not to break confidentiality and inform the family GP and or emergency social services.

Potential for coercion and or inducement

Free treatment may persuade some parents to seek osteopathic care where in other circumstances they may not consider it. Conversely it may increase equity (access) and therefore promote equality in care provision, as the traditionally white and middle class osteopathic clientele could be expanded to include other groups (C. A. Fawkes et al., 2014; Vaucher et al., 2018). All parent participants will be given written information supported by verbal information where requested and the study teams will be available to answer any questions potential participants might have. A 24 hour cooling off period will be given between the participant invitation and the final consenting process to be in the trial. Consent will be gained and counter signed via the treating osteopath, the consenting procedure will be addressed in the osteopath training course and in the Protocol for Osteopaths. Specific wording is given to reduce the potential for coercion giving the parent complete freedom to decide without quality of care being affected. If the parent feels induced by the free treatment we will ask the osteopaths to point out that they parent will be required to complete 2 questionnaire and complete a 14 day crying diary.

Information protection

Only the clinic staff and research staff (subject to the appropriate consent) will be able to view the infant's trial records. Initial contact will mostly be via osteopaths and, or an experienced member of the study team. Parents will have the choice whether or not to participate. All data will be collected using CastorEDC, a GDPR compliant solution designed for clinical trials by Ciwit B.V. and hosted in the Netherlands (ISO/IEC 27001 – 0025833).

7.2 Risk-benefit assessment

Risks for participants

In Switzerland, one infant in two are seen by an osteopath during its first year of life. One of the most frequent motives is unsettled crying. Osteopathic care is therefore perceived as usual care for infants with colic even if there is no evidence of the added value of hands on treatment with the intention of altering tissues. Parents usually seek osteopathic care for its interpersonal reassuring character (Gardner, 2011). A survey in the Netherlands collected information on adverse events following manual treatment in 785 children seeing by 27 osteopathic practitioners. 13% of paediatric patients experienced side effects which were recognised as being non-serious and with minor consequences of short duration (i.e. crying, changes in sleeping habits, restlessness). No serious or mild adverse events were observed (Kales, 2011). When broadening

investigations of adverse events to all forms of manual treatment, a systematic review identified 9 cases of severe adverse events following paediatric spinal manipulation over a 58-year period (Vohra et al., 2007). Spinal manipulation in infants is however not part of what is proposed to infants during osteopathic paediatric care. No serious adverse events associated to osteopathic care were observed in small clinical trials studying effects of osteopathic care on colic, representing 116 infants who received treatment (Carnes et al., 2018). To our knowledge, there are but two reported cases of severe fatal complications following manual therapy with excessive force. Both were due to respiratory depression. One took place following spinal manipulation (Holla et al., 2009), the other following cranio-sacral therapy (Brand et al., 2005). Both cases were related to negligence, unusual osteopathic paediatric manual care, and due to the use of techniques that are against actual recommendations. The incidents of such events remain very rare and are believed to occur in less than one infant in 2.5 million.

The safety of manual therapy care in infants has been the subject of review (Carnes, Mars, et al., 2010; Dobson et al., 2012; Todd et al., 2015). As exposed in the previous paragraph, the reported incidence and prevalence of moderate and serious adverse events is very low with this form of gentle light touch therapy. Manipulation using manual thrust techniques are contra-indicated in this patient population and none will be used in this study. This study is expected to be a very low risk of harm in both arms of the trial especially as the treatment is very gentle and the condition is usually self-limiting and resolving.

There is a burden to the parent to complete the baseline and follow up questionnaires , these will take around 10 minutes to complete. The crying diaries present more of a burden but have been shown in previous studies to be feasible, useful and accurate to within 5 minutes (Barr et al., 1988; Ellis-Davies et al., 2012). They will take around 5 minutes to complete per day.

There is a possibility that the Karitane Questionnaire about Parenting Confidence (15 questions), may be upsetting for some parents. The baseline questionnaire containing this questionnaire will be completed in the osteopathic clinic just prior to randomisation so if the parent is distressed at all the osteopath will be there to help manage the situation and offer support. The questionnaire will be repeated at 14 days, the parent will be able to call the osteopath or the research study team if they have any problems.

There may also be a travel burden and travel cost to visit the osteopathic clinic.

Benefits for participants

The potential benefit to the parent is free osteopathic care and support which would otherwise incur a fee. However in return we are asking the parent to complete 2 questionnaires and keep a 14 day crying diary.

Risks and benefits for participating osteopathic clinicians

Some osteopaths may be conflicted about giving the control intervention as it is not a treatment they may normally deliver to these infants. We have ensured in the design of the trial that the infants and parents will be given best usual advice and receive light touch which can also have some limited beneficial outcome. To prove effectiveness of any intervention there is a need for a control intervention, particularly important in this trial as there is a strong regression to the mean as ‘colic’ is normally a time limiting condition, hence we propose to recruit and treat infants within

their first 12-week period of life, as after this time crying tends to settle. In addition, the infants being treated are not ill. The potential harm is more likely from a poorly coping parent than from the colic itself. The osteopath will help the parents with coping in both arms of the trial. Osteopaths who are not able to, or who are uncomfortable delivering the control intervention will not be included in the trial.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

Auditing, Quality control, fidelity and intervention treatment drift

All osteopaths (co-investigators) will be trained and required to complete case history tracking forms to ensure that case histories and screening procedures are similar in each group. In addition, during the treatment delivery phase, 50% of the infant patient records will be checked by the study team for any protocol deviations.

Web-based internal audits will be run with every secondary site during the first two months of data collection. In Switzerland, with the participant's consent, each osteopath is to film one of their intervention for visual and audio assessment of fidelity to protocol. Data entry is monitored by the data manager who weekly reports recruitment rate and quality of entered data. Double data entry is to be used for transferring data from paper forms.

The study has its own independent Data Monitoring Committee (DMC).

External audits

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

No copy of the aggregated data will be kept in Switzerland. The UCO holds responsibility for managing data and archiving data for the international study. Most data is captured directly electronically using CastorEDC. This dedicated system for capturing clinical trial data will capture and manage all data apart for Consent forms, Participant Logs and Crying Diaries.

The Consent Form will be stored in the treating osteopath's patient note file and an additional copy will be kept by the parent. Participant Logs, including names and contact details, are kept by co-investigators. Number of parents invited to participate and refusals are anonymised and summarised to be reported to the Principle Investigator. Transfer from paper forms diary entries to the CastorEDC will be done by the Chief Investigator for data quality control. Double data entry by a second person is planned to detect and avoid transcription errors.

CastorEDC

The software (CastorEDC https://castoredc.com), developed by Ciwit B.V, in the Netherlands, provide facilities for electronic case report forms, survey questionnaire data capture and participant case history tracking information.

Castor complies with all applicable laws and regulations, including ICH E6 Good Clinical Practice (GCP), 21 CFR Part 11, EU Annex 11, General Data Protection Regulation (GDPR), HIPAA (US), ISO 9001 and ISO 27001. By using Castor, researchers are enabled to comply with these laws and regulations. Castor is a validated system and approved by external auditors. Trevalco audited Castor EDC in November 2017 for GCP compliance to ensure compliance (ISO/IEC 27001 – 0025833).

Confidentiality

Anonymity of the participants is ensured through the allocation of a unique study identifier. Confidentiality and blinding are ensured by access controls set by the study data manager. Co-investigators have access to all entries within sites. They however can only access to files related to participants they are following.

Backup and storage

All data throughout the trial period is stored on the secure and backed up CastorEDC servers which complies with current EU and UK legislation and standards. All data access and changes are tracked and logged. All study material and details including the final anonymised data set will be archived and stored in a university repository for 25 years.

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

CastorECD automatically attributes a code to each participant. They are generated sequentially and automatically by Castor EDC for each site (Switzerland is a single site). The format is XXXNNNNN where XXX is an institution code and NNNNN is the number part. There is no way to know what time and day it was generated purely from the code.

The data collected up to the withdrawal of the study will be used, so as not to compromise the value of the study as a whole.

Participation identification lists are stored by co-investigators. These lists also include contact details such as telephone numbers and E-mail addresses. Each co-investigator is responsible of keeping a secured paper form list of participants they have recruited. Upon completion of the trial, for future legal purposes, the participant list linking IDs to patients are archived by co-investigators. Consent forms are to be kept for at least 25 years with the patient record.

Practitioners do not have access to participant questionnaires. Chief and principal investigators have access to the coded electronic data. Once cleaned by the UCO data clerk, anonymised data is to be made available to the statistician.

Data made available to co-authors or reviewers are coded and not given in sufficient detail to be able to identify participants.

8.4 Retention and destruction of study data

All study data are archived in the UK for 25 years after study termination or premature termination of the study except for participating identification lists who will be stored locally at recruiting sites.

9 MONITORING AND REGISTRATION

Monitoring

The study will be run and implemented by the Principal Investigator and the trial management team who are responsible for ensuring the study is implemented and run in accordance with the sponsors' requirements and law pertaining to medical research on human tissue and subjects.

In Switzerland, due to the COVID-19 situation, distant secondary sites visits are planned in prior and after the start of the study. A first visit is planned 1-2 weeks prior to patient recruitment. This visit aims to assess the adequacy of the procedure put into place. A second is planned within the first month of recruitment. Phone interviews with the secretary and the osteopaths are to be planned. The verification process is then done with the principal investigator and the osteopath practitioner who verify procedures whilst being online.

The following elements are to be verified:

- Recruitment method (placement and use of official material)
- Respect of 24h delay prior to recruitment (interview and random verification)
- Signed copy of informed consent
- Respect of the allocation procedure
- Annotation in patient record
- Security and completion of participant log
- Management of paper-form CRFs
- Access to co-investigator brochure and material.

Oversight and governance of the trial has been set by the Trial Steering Committee (TSC) and is composed of specialists who are independent from the Trial Management Committee (TMC). The TSC includes a medical practitioner, a paediatric specialist, a statistician, a research specialist in trials and a lay representative. The principal investigator will report to the TSC as required. The Data Monitoring Committee DMC will be convened once 75 infants have been recruited and or earlier if required by the TSC to review the trial data and or any serious ethical issues that arise. The DMC will consist of an independent academic researcher, statistician and the trial data manager.

Any substantial change to this protocol will be proposed and managed by the TMC, approved by the TSC and submitted for approval to the relevant Ethics Committees and then amended on the trial registry.

Data entry monitoring is under the reasponsability of Dawn Carnes, data quality entry is done by Kevin Brownhill in the UK, quality control for logs, consent forms and protocol fidelity is done by Paul Vaucher.

Data will be held confidentially in line with ethical and statutory expectations for a minimum of 25 years by the main sponsor institution (University College of Osteopathy). Participants' parents will

be informed of the process whereby they or their children, when adults, may seek to review their data from the archive.

Study registration

The study is registred in a registry listed in the WHO International Clinical Trials Registry Platform (ACTRN12620000047998). It is also registered in French on the Swiss National Clinical trial Portal.

Audits

Swiss Ethics is authorised to audit the trial for data collected in Switzerland. They have access to local source data and documents. During audits, the sponsor reserves the right to request coordination of procedures with the London-Surrey National Health Service Research Ethics Committee to gain access to the electronic CRFs based in the UK. National principal investigators are available to answer all questions during monitoring.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

Funding

Financial funding was received from the overall project from the National Council for Osteopathic Research Board of Trustees and The Osteopathic Foundation. In Switzerland, funding was obtained from the Swiss Osteopathic Science Foundation and from the HES-SO. Other indirect and direct support was received from the Sponsor organisation, University College of Osteopathy and the School of Health Sciences Fribourg for Switzerland.

Publications

Publications are written collectively under the leadership of the chief investigator. All authors have full access to anonymised data for verification. Publications using data from the study need approval from the consortium. Authorship are defined by the ICMJE criteria.

Conflicts of interest

The Swiss Primary Investigator has an accessory occupation as an independent osteopathic practitioner.

Written agreement

The collaboration between the University College of Osteopathy and the School of Health Sciences Fribourg is settled in a written agreement form signed by both parties. The University College of Osteopathy holds responsibility for the planning, execution, coordinating and the management of the entire study. The Swiss Sponsor is responsible the executing of the protocol in Switzerland.

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Legal documents and guidelines for clinical trials in Switzerland

1. Common Terminology Criteria for Adverse Events (CTCAE)
   https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
2. Declaration of Helsinki
   https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
3. Federal Act on Data Protection (FADP)
   https://www.admin.ch/opc/en/classified-compilation/19920153/index.html
4. Human Research Act (HRA)
   https://www.admin.ch/opc/de/classified-compilation/20061313/index.html
5. International Conference on Harmonization (ICH) E6(R2) Guideline for Good Clinical Practice
   http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf
6. International Conference on Harmonization (ICH) E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
   http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf
7. Ordinance on Clinical Trials in Human Research (ClinO)
   https://www.admin.ch/opc/de/classified-compilation/20121176/index.html

11 CHANGE HISTORY

Version Nr	Version date	Modified without version change	Description, comments	Control
1.0	14.12.2020		Initial version	PV
1.1	07.01.2021		Changed data collection method from paper to CastorECD with added French and German versions.	PV
1.2	15.02.2021		Modifications following ethical review	PV, DCA, SVO, NVP