Journal Pre-proof

Crying Unsettled and disTressed Infants Effectiveness Study of osteopathic care (CUTIES trial): Pragmatic randomised superiority trial protocol

D. Carnes, P. Bright, K. Brownhill, K. Carroll, R. Engel, S. Grace, S. Vogel, P. Vaucher

PII: S1746-0689(20)30052-3

DOI: https://doi.org/10.1016/j.ijosm.2020.08.001

Reference: IJOSM 552

To appear in: *International Journal of Osteopathic Medicine*

Received Date: 19 March 2020

Revised Date: 17 August 2020

Accepted Date: 20 August 2020

Please cite this article as: Carnes D, Bright P, Brownhill K, Carroll K, Engel R, Grace S, Vogel S, Vaucher P, Crying Unsettled and disTressed Infants Effectiveness Study of osteopathic care (CUTIES trial): Pragmatic randomised superiority trial protocol, *International Journal of Osteopathic Medicine* (2020), doi: https://doi.org/10.1016/j.ijosm.2020.08.001.

Title, author, trial registration and ethics information

Crying Unsettled and disTressed Infants Effectiveness Study of osteopathic care (CUTIES trial): Pragmatic randomised superiority trial protocol.

Carnes D, Bright P, Brownhill K, Carroll K, Engel R, Grace S, Vogel S, Vaucher P.

Corresponding Author: Dawn Carnes

Dawn Carnes
Professorial Research Fellow, University College of Osteopathy, 275 Borough High St, London. SE1 1JE.
Telephone: +44 (0) 20770895330
Email: dawn.carnes@uco.ac.uk
Invited Professor
Faculty of Health, University of Applied Sciences Western Switzerland, 16a Rue des Arsenaux, 1700 Fribourg
Email: dawncarnes@hefr.ch
ORCID: 0000-0002-3152-3133

Philip Bright
Head of Research and Professional Development, European School of Osteopathy, Boxley House, Maidstone, Kent
Email: philbright@eso.ac.uk
ORCID: 0000-0002-5339-8281

Kevin Brownhill
University College of Osteopathy, 275 Borough High St, London. SE1 1JE.
Telephone: +44 (0) 20770895330
Email: kevin.brownhill@uco.ac.uk

Karen Carroll
Amersham Osteopathic Clinic, Chiltern Rd, Amersham, Bucks.
Telephone: 01494 434651
Email: amershamosteo@me.com

Roger Engel
Macquarie University, Balaclava Rd, Macquarie Park NSW 2109
Telephone : 61 2 9850 6387
Email: roger.engel@mq.edu.au
ORCID: 0000-0001-6021-0497

Sandra Grace
Southern Cross University, Military Rd, East Lismore. NSW 2480
Telephone : 61 2 6620 3646
Email : sandra.grace@scu.edu.au
ORCID : 0000-0002-0300-4088

Steven Vogel
University College of Osteopathy, 275 Borough High St, London. SE1 1JE.
Telephone: +44 (0) 20770895330

Paul Vaucher
School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland
paul.vaucher@hes-so.ch
ORCID: 0000-0002-0652-0985

Protocol Version. V1.15 11.3.20

Ethics approval: London-Surrey National Health Service Research Ethics Committee: IRAS # 268925 19/LO/1620 (09.11.19)

Trial Registration: ACTRN12620000047998

Crying Unsettled and disTressed Infants Effectiveness Study of osteopathic care (CUTIES trial): Pragmatic randomised superiority trial protocol.

Abstract

Background: Infants who excessively cry, are distressed and unsettled can have a marked impact on family life. One form of support is manual therapy and osteopathic care. There is, however, limited research and debate about the effectiveness of manual therapy and osteopathic care for these infants.

Aim: To evaluate the effectiveness of osteopathic light touch manual therapy care for excessively crying, unsettled and distressed infants.

Method: We propose a two-arm pragmatic randomised controlled trial, 112 infants will be randomised to either: i) Specific osteopathic light touch manual therapy with best practice advice and support or, ii) Non-specific light touch with best practice advice and support. Parents will be blinded to group allocation.

Population: Healthy infants under 10 weeks old, reported by their parents as excessively crying, fussing, unsettled, distressed and difficult to console using the Rome IV criteria (> 3 hours of crying per day, for 3 days or more, for 1 week or more). Infants with diagnosed health conditions for which they are receiving medical treatment or who are unsuitable for osteopathic care will be excluded from the study.

Outcomes: The primary outcome is reduced infant mean crying time over 14 days, collected via parent reported diaries. Secondary outcomes are: i) Parental self-efficacy, ii) Parent perceived global improvement, iii) Satisfaction and experience with treatment, iv) Adverse events, and v) Direct cost.

Discussion: The results from this study will provide information that osteopaths, other health care professionals and parents can use to inform their decisions about treatment choices.

Keywords

Unsettled infants, crying, colic, osteopathy, manual therapy, randomised controlled trial, light touch

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).

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 United Kingdom (UK), we estimate that the number of infants seen by osteopaths is around 61,000 per annum (extrapolated from data in Fawkes *et al* 2013 and from the General Osteopathic Council website) 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)). It is estimated that around 8-9% of all osteopathic consultations are for those between 0-1 years (Osteopathic International Alliance 2013).

Osteopathic treatment for 'colicky' infants commonly involves gentle touch and movement (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 2011). 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 2011).

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 (Lim 2006; Cowie 2013) 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 (Giandomenico *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

that this type of gentle light touch therapy has a low risk of harm (Carnes *et al* 2018) and that adverse events reported were transient and low to moderate in severity (Prevost *et al* 2019). However, more scientifically robust definitive trials on the topic are needed to clarify the situation.

Aim

The aim of this study is 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 is not intended to produce evidence about the underlying mechanism of action of osteopathic care, but will provide data regarding the belief of both osteopaths and parents, that the 'therapeutic intent' associated with the directed osteopathic light touch is the active element in delivering benefits.

Method

We recognise that parents 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. We have therefore designed this study 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 (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 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 of infants in such a group.

Design

A pragmatic two arm multicentre randomised superiority effectiveness trial design will be used to compare osteopathic usual care manual therapy and advice and non-specific light touch and advice in infants under 10 weeks old who excessively cry, are distressed, unsettled and/or fussing and are difficult to console. The protocol manuscript has been informed by adherence to the Spirit Clinical Trial Protocol statement and associated guidance (Chan *et al* 2013; Chan *et al* 2013).

Infants in the intervention arm will receive usual osteopathic manual therapy treatment with best practice advice and support while infants in the control group will receive non-specific light touch with best practice advice and support. Best practice advice will be drawn from the national UK guidance (NICE 2017, https://cks.nice.org.uk/colic-infantile)

We hypothesise that specific targeted osteopathic light touch usual care is superior to non-specific light touch.

All infants and parents will receive best practice advice and support. This approach should encourage recruitment as all infants will receive a standard health screen and parents will be able to discuss issues and be given advice, regardless of group allocation. By providing psychological and social support and reassurance to all infants and parents enrolled in the study, this study will meet the ethical requirements for research that involves parents who may be vulnerable when dealing with excessively crying infants. All infants enrolled in the trial will be treated at no cost.

Participants, interventions and outcomes

Setting

The trial will have sites in two countries: the UK and Australia. Both private osteopathic clinics and osteopathic education clinics will be used. We estimate that we will need 5 - 10 sites and around 20 osteopaths to recruit and deliver the interventions.

Participants - Eligibility criteria

Inclusion criteria

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 (Zeevenhooven *et al* 2017).

Exclusion criteria

Infants will be excluded if they have active co-morbidities that require medical attention or treatment prior to enrolment. This will ensure that the infants recruited are healthy and thriving and that osteopathic care is appropriate.

Infants who have no tension in their bodies as palpated by the osteopath and are therefore unlikely to benefit from osteopathic treatment will also be excluded. Infants who have already received osteopathic treatment will be excluded, but we will not exclude infants who have had or seek other forms of non-physician based care prior to or during the study, unless they are no longer healthy enough to be included (we will however collect information about additional care and adjust for it in the final analysis).

Infants will also be excluded from the trial if their parent is unable to provide informed consent or is not sufficiently fluent in English to be able to fully comprehend the trial literature and/or complete the crying diary and questionnaires.

Interventions

Specific light touch intervention 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 during the treatment. This arm is called the Targeted Tension Release arm or TTR group. 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

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.

Non-specific light touch intervention arm

Infants randomised to the non-specific light touch intervention arm, will be given a non-specific generic light touch attention control intervention for approximately 10-20 minutes. Predetermined protocolised general information will be communicated with the parent 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, to distract themselves from receiving any palpatory information and consequently responding with any treatment. *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 intervention 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 5 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/legal guardian 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 verbally and in the form of an information leaflet or an online URL, depending on the preference of the parent. 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. 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 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

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 that they would like to gently touch the infant with the aim of reducing tissue tension.

Targeted light touch and non-targeted light touch may modulate tissue tension tone. 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* 2009) and other studies that show there are contextual beneficial elements of care involving touch (van den Hoogen *et al* 2017, Meltzoff *et al* 2018). 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.

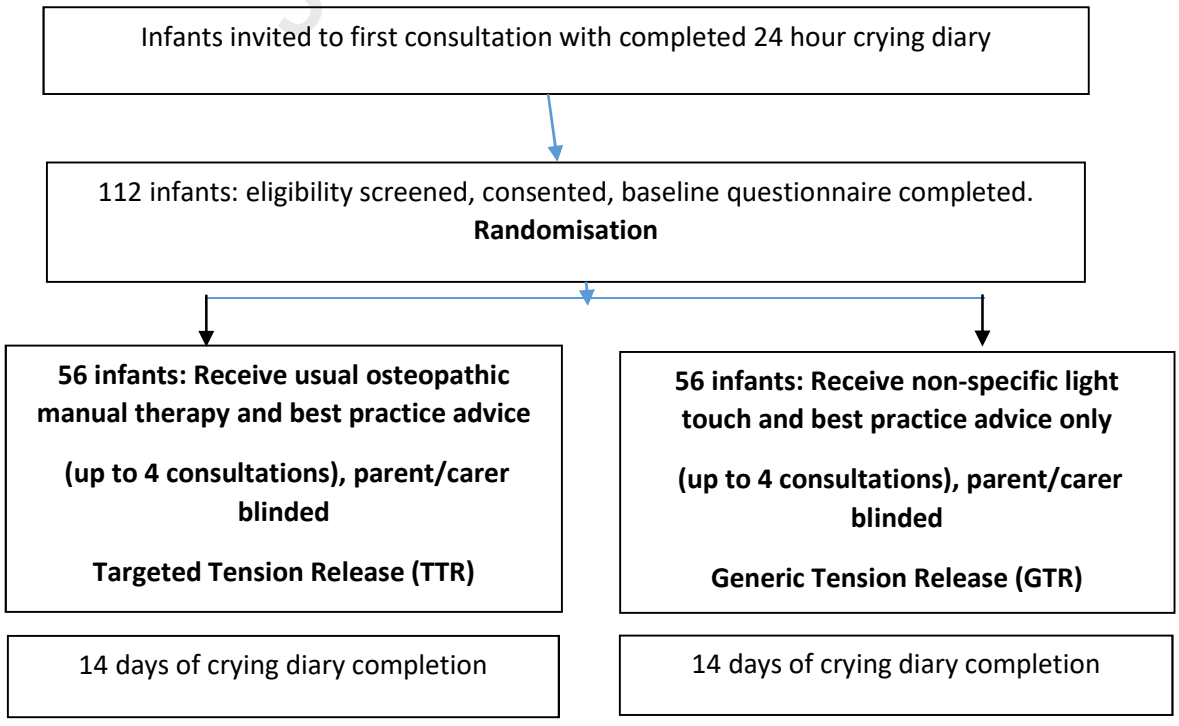
Parents will not be asked to desist from using any other care strategy during the trial period.

Outcomes

The primary outcome in the trial is average daily crying time over 14 days. 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). In that study, the 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.

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 at day 14, adverse events data and basic direct cost of treatment.

Diagram 1. Study scheme flow chart



Day 14 parent follow-up questionnaires	Day 14 parent follow-up questionnaires

Post trial care will be delivered as normal within the parent's clinic of choice.

Pilot study

A pilot feasibility study was conducted 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 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.

Sample size

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 (Table 2). This sample size calculation is conservative because it disregards the fact that there are repeated measures for each infant and that the model will be corrected for the baseline crying time value. Thus, the actual power will be higher.

Table 2: Sample size estimates without loss to follow up.

	MCID (daily reduction in crying time in minutes)			
Power	**10**	**15**	**30**	**60**
0.8	n=636	284	72	18
0.9	n=852	380	**96**	24
0.95	n=1054	468	118	30

We estimate that approximately 400 - 500 parents/carers will need to be approached in order to recruit 112 infants.

Recruitment and consenting procedures

Infants and their parents will be recruited directly via the recruiting osteopathic clinics or indirectly through posters or referrals from midwives, pre-natal and ante-natal groups, who may hear about the trial through word of mouth, social media and/or promotional posters.

When a parent with a crying, distressed and unsettled baby calls the clinic to book an appointment, the osteopath (or the receptionist) will ask the parent if the baby meets the inclusion criteria, the osteopath (or receptionist) will inform the parent 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 and the outcome. Those who are not interested in participating in the trial will be booked an appointment as per normal clinic procedures and where possible the reason for decline will be recorded anonymously. 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 date. 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.

When an interested parent attends their scheduled consultation they will be given the chance to ask questions about the study and asked if they still want to participate in the trial. The infant will be enrolled in the trial and given a unique identification study number (ID) if they meet the inclusion criteria and have consent. The parent 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.

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 Procedures

All trial information will be sent a minimum of 24 hours prior to the parent and infant consultation. The first consultation will provide the opportunity for parent/guardians to ask any outstanding questions to help them make an informed final decision to consent to participate. The biological parent or legal guardian parenting the child will be asked to sign the consent forms and the recruiting osteopath will counter-sign to confirm the consent is valid and informed. The parent or legal guardian will keep one copy and the other will be retained by the osteopath.

Recruiting and training trial osteopaths

Volunteer osteopaths will be recruited via their professional associations, osteopathic educational institutions, specialist clinics and existing osteopathic paediatric interest groups. The osteopaths will be trained to deliver the trial interventions as per protocol.

All osteopaths must be registered with their osteopathic professional statutory regulatory body and insured and must have experience treating infants with an average of one infant per week for a minimum period of one year. They will have to have access to the internet in their clinical setting and agree to undergo the training in the trial's protocol to participate in the trial.

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/guardian and procedures for recording

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.

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.

Assignment of interventions

Randomisation Procedures

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. The principal investigator will be blinded to allocation, but the data manager who will have no contact with participants will not be blinded.

Blinding

Parents will be blinded to group allocation (*i.e.* they 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 TTR or GTR intervention.

There will be a standardised communication protocol between the osteopath and the parent during both the TTR and GTR 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 will be present throughout the treatment session and free to observe the delivery of intervention. However, parents will remain 'blinded' throughout the active phase of the trial so that outcomes are not biased *a priori* by parent 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 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.

Data collection and management

Schedule of Treatment and assessment

Prior to the first treatment, a parent will complete a baseline questionnaire, including a parenting confidence questionnaire, and a 24-hour crying diary. Osteopaths will be encouraged to build rapport with each parent 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) of the infant. Parents 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.

Follow-up Procedures

All participating parents will receive a 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.

Participant Data Collection and Follow-up

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 Karitane : Confidence in Parenting questionnaire* Parent 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.	Karitane: Confidence in parenting questionnaire * Parent satisfaction and experience with osteopathic treatment 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)

The osteopaths will be required to record the following information:

- Osteopath age, sex, education and number of years post-graduation
- Number of treatments given for each participant
- Type of treatment given (at each consultation)
- Duration of each treatment
- Adverse events (none, mild, moderate, severe)
- Additional comments considered relevant by osteopath

We will use the Karitane Parents' Confidence Questionnaire as it has been specifically designed and tested in our population of interest (*i.e.* parents/carers with infants rather than toddlers and children (Crncec *et al* 2008). We will use Cronbach alpha =.81, test re-test reliability r=.88, Sensitivity 86% and positive predictive value 88%.

We will use standard global change and satisfaction questions as used and tested for reliability and validity in the National Council for Osteopathic Research (NCOR) Patient Reported Outcome Measures (PROM) app and online data capture system (Fawkes *et al* 2013; Froud *et al* 2018)

Data management

All data will be captured and stored electronically, with the exception of the trial consent forms, one copy will be stored in the treating osteopaths patient note file and an additional copy will be kept by the parent.

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 Castor server which complies with current EU and UK legislation and standards.

All study material and details including the final anonymised data set will be archived and stored in a university repository for 25 years.

Statistical Analysis

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.

Description of study population

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.

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).

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.

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.

Monitoring

Auditing, Quality control, fidelity and intervention treatment drift

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.

Stopping rules

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.

Adverse events

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 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.

Ethics, governance, patient and public involvement and dissemination

Ethics

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).
The Australian arm of the trial received ethics approval from Southern Cross University Human Research Ethics Committee (HREC), approval number 2019/569.

Public and Participant Involvement

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 will also sit on the trial management committee and the trial steering committee.

Governance

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. Oversight and governance of the trial will be by a Trial Steering Committee (TSC) composed of specialists who are independent from the Trial Management Committee (TMC). The TSC will include 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

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 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 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.

The sponsor will provide insurance for the study.

Discussion

The design of this study reflects the challenges of researching complex interventions in a real-world setting. These complexities include difficulties around conducting randomised trials, maintaining participant blinding and recruiting parents who may be vulnerable and desperate for help in caring for their infant. The condition of 'colic' is not life threatening but it is distressing for both the infants and their parents. The design of this trial will enable us to distinguish between the effect of touch with and without treatment intent.

The willingness of osteopaths to deliver both forms of intervention is challenging. All osteopaths will be asked at the end of their training about their experience in participating in the trial. If they are uncomfortable about delivering the control intervention they will be free to leave the study. Those that choose to participate will understand the need to deliver the interventions as per the protocol and invite all parents/guardians of eligible infants into the trial. We expect the osteopaths to be sufficiently professional to deliver every aspect of care appropriately and at the standard expected of a heath professional. There is potential for over-compensation of advice, guidance and support in the control arm which may enhance the contextual aspects, but if the trial shows a favourable difference in the osteopathic care arm we will know that the effects of the manual therapy with intent are superior to these contextual components of care.

We hope that the results from this study will provide information that osteopaths, other health care professionals and parents can use to inform decisions about treatment choices for infants who excessively cry, are irritable, distressed and difficult to console.

References

Barr RG, Kramer MS, Boisjoly C, McVey-White L, Pless IB. Parental diary of infant cry and fuss behaviour. Arch. Dis. Of Childhood. 1988: 63; 380-387

Berkowitz CD. Physical Abuse of Children. N. Engl. J. Med. 2017 Apr 27;376(17):1659-1666

Carnes D, Plunkett A, Ellwood J, Miles C. Manual therapy for unsettled, distressed and excessively crying infants: a systematic review and meta-analyses. BMJOpen 2018; 8:e019040

Connectivity Is Modified by the Operator's Tactile Attention. Front Hum Neurosci. 2017; 11: 368 https://doi.org/10.3389/fnhum.2017.00368

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ 2013;346:e7586.

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200-207.

Cowie J. Managing infant colic: A literature review. *Primary Health Care*. 2013; 23(2): 16-20.

Črnčec R, Barnett B, Matthey S. Development of an instrument to assess perceived self-efficacy in the parents of infants. Res Nurs Health. 2008 Oct;31(5):442-53. doi: 10.1002/nur.20271.

Črnčec, R., Barnett, B., & Matthey, S. Karitane Parenting Confidence Scale: Manual. Sydney South West Area Health Service. 2008. Sydney: Australia. http://www.preventchildabusenj.org/newsletters/hf_weekly/kpcs_manual.pdf

Dobson D, Lucassen PLBJ, Miller JJ, Vlieger AM, Prescott P, Lewith G. Manipulative therapies for infantile colic. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD004796. DOI: 10.1002/14651858.CD004796.pub2

Fawkes C, Leach J, Mathias S, Moore A. A profile of osteopathic care in private practices in the United Kingdom: a national pilot using standardised data collection. Man Ther. 2014 Apr;19(2):125-30. doi: 10.1016/j.math.2013.09.001. Epub 2013 Sep 13.

Field T, Diego MA, Hernandez-Reif M, Deeds O, Figuereido B. Moderate versus light pressure massage therapy leads to greater weight gain in preterm infants. *Infant Behav Dev*. 2006;29(4):574-578. doi:10.1016/j.infbeh.2006.07.011

Froud R, Fawkes C, Foss J, Underwood M**,** Carnes D. Responsiveness, reliability, and minimally important and minimal detectable change of three electronic patient reported outcome measures for low back pain: a validation study. J Med Internet Res. 2018 Oct 24;20(10):e272. doi: 10.2196/jmir.9828.

De Giandomenico A, Cerritelli F, Cortell P. Sensitization and Interoception as Key Neurological Concepts in Osteopathy and Other Manual Medicines Front. Neurosci. 2016; 10:100 https://doi.org/10.3389/fnins.2016.00100

Hiscock H, Jordan B: 1. Problem crying in infancy. Med J Aust 2004, 181(9):507-512.

Jäkel A, von Hauenschild P. Therapeutic effects of cranial osteopathic manipulative medicine: a systematic review. J Am Osteopath Assoc. 2011 Dec;111(12):685-93.

Johnson JD, Cocker K, Chang E: Infantile Colic: Recognition and Treatment. Am Fam Physician 2015, 92(7):577-582.

Kato N. Prevalence of Infant Shaking Among the Population as a Baseline for Preventive Interventions. J Epidemiol. 2016; 26(1): 2–3.

infancy. *Journal of Alternative & Complementary Medicine*. 2009; 15(4), 341-345.

Kurth E, Spichager E, Cignacco E, Powell kennedy H et al. Predictors of crying problems in the early postpartum period. JOGNN, 2010, 39: 250-262

Leuchter, Russia Ha-Vinh; Darque, Alexandra; Hüppi, Petra Susan Brain Maturation, Early Sensory Processing, and Infant Colic, Journal of Pediatric Gastroenterology and Nutrition: December 2013 - Volume 57 - Issue - p S18–S25, doi: 10.1097/01.mpg.0000441929.05684.78

Lim KW. Infantile colic: a critical appraisal of the literature from an osteopathic perspective. International Journal of Osteopathic Medicine. 2006; 9(3), 94-102.

Meltzoff A, Ramirez RR, Sabi J, Larson E, Taulu S, Marshall PJ. Infant brain responses to felt and observed touch of hands and feet: an MEG study. Developmental Science. 2018; DOI: 10.1111/desc.12651

Morris S, James-Roberts IS, Sleep J, Gillham P: Economic evaluation of strategies for managing crying and sleeping problems. Arch Dis Child 2001, 84(1):15-19.

National Institute for Health and Care Excellence. Colic – Infantile, Scenario: Management of infantile colic. 2017 ; [Accessed 14-02-2020] https://cks.nice.org.uk/colic-infantile#!scenario

Osteopathic International Alliance. Osteopathy and Osteopathic Medicine: A global view of practice, patients, education and the contribution to healthcare delivery. 2013; http://oialliance.org/wp-content/uploads/2014/01/OIA-Stage-2-Report.pdf [accessed 29.6.20]

Prevost C.P, Gleberzon B, Carleo B, Anderson K, Cark M, Pohlman K.A. Manual therapy for the pediatric population: a systematic review. *BMC complementary and alternative medicine*. 2019. *19*: 60.

Sung V. Infantile colic. Aust Prescr. 2018; 41(4):105-10.

Van den Hoogen A, Teunis CJ, Shellhaas RA, Pillen S, Benders M, Dudink J. How to improve sleep in a neonatal intensive care unit: A systematic review. Early Human development. 2017, 113(Oct): 78-86

Vickers A, Ohlsson A, Lacy J, Horsley A. Massage for promoting growth and development of pretermand /or low birth-weight infants. Cochrane database systematic reviews 2004 Issue 2 Art no CD0000390

Wolke D, Bilgin A, Samarra M. Systematic review and meta-analysis: Fussing and crying duration and prevalence of colic in infants. J Pediatr. 2017 Jun; 185:55-61.e4. doi: 10.1016/j.jpeds.2017.02.020.

Zeevenhooven J, Koppen IJN, Benninga MA. The new Rome IV criteria for the functional gastrointestinal disorders in infants and toddlers. Pediatr Gastroenterol Hepatol Nutr 2017; 20 (1):1-13

Conflict of interest, funding and sponsor statements

Conflicts of interest: DC is the director of the National Council of Osteopathic Research. She developed the proposal for the study, but had no involvement in the decision by the trustees of the National Council of Osteopathic Research charity to fund the study. DC is employed by the Sponsor Organisation, University College of Osteopathy, to lead the trial. SV is a trustee of the National Council of Osteopathic Research and also a sponsor – investigator for the trial on behalf of the Sponsor organisation University College of Osteopathy. He had no involvement and withdrew from the decision making process by other trustees of the National Council for Osteopathic Research having declared a potential conflict of interest. SV, DC and RE are Editors of the International Journal of Osteopathic Medicine but had no role in the review process or decision to publish this manuscript.

Funding: Financial funding was received from the National Council for Osteopathic Research and The Osteopathic Foundation. Material and other indirect and direct support was received from the Sponsor organisation, University College of Osteopathy. The Australian arm of the trial was funded by an industry grant from Osteopathy Australia with additional funding from the Sutherland Cranial Teaching Foundation of Australia. None of the financial funders had any role in the design, development of editorial contribution to the manuscript at any stage and will not have any role in the trial's execution, analysis, interpretation of the data or decision to submit or disseminate results of the study.

Sponsor: Steven Vogel, Deputy Vice Chancellor (Research), Sponsor-Investigator, University College of Osteopathy, 275 Brough High Street London SE1 1JE. Email: Steven.Vogel@UCO.AC.UK