APPENDICES

Appendix 1: Protocol Changes & Notes

Date **Section of Protocol** Type of amendment*	**Original Version**	**New Version** Justification
02/21/2023	Inclusion criteria for study design allowed for RCTs and prospective cohort studies.	Inclusion criteria for study design amended to only RCTs. Although prospective cohort study designs provided evidence for an association between the intervention and the outcome, these studies often lacked a clear control group making it difficult to distinguish the treatment's impact on our primary outcomes in comparison to a placebo or sham procedure.

Appendix 2: Inclusion Criteria Table & Outcomes of Interest

Study Inclusion Criteria

Category	**Inclusion Criteria**	**Justification/explanation**	**Order**
Study design	Randomized controlled trials (RCTs)	RCTs are the gold standard for evaluating interventions and provide strong causal evidence linking intervention and outcome.	1
Population	"Patients with Crohn's Disease"	Patients with mild-to-moderate Crohn's Disease often have painful flare-ups that negatively affect their quality of life.[51] There exists little evidence that current first-line treatments affect disease course and are effective in maintaining clinical remission for patients with mild-to-moderate CD.[14] Because of this, there are limited treatment options for individuals with mild to moderate CD.[4,14]	2
Intervention/ Exposure	"Traditional Chinese Medicine (TCM)"	TCM consists of a wide variety of treatments.[25] However, for this systematic review, TCM refers to a class of treatments including methods such as traditional Chinese herbs (i.e., Fufangkushen, Tripterygium wilfordii Hook F), moxibustion, cupping, and acupuncture.[25] These measures remain relatively unexplored in the context of chronic gastrointestinal illnesses but have shown some promise in pain management.[25]	3

Comparison Condition	Placebo or sham procedure	Placebo treatment is the application of a treatment that has no therapeutic value. Using a placebo to compare against the treatment can decrease bias and more accurately evaluate the applied treatment's efficacy.[26] Placebos have been evaluated against acupuncture and found varying effectiveness of acupuncture for pain management when compared to sham acupuncture.[26]	4
Outcome	Change in Crohn's severity	Our primary outcome - change in objective measures of Crohn's severity (Measured by CDAI or CDEIS). These index scores are used because CDAI and CDEIS are direct measurements of symptom severity. Because severity is related to symptom improvements and a better quality of life, this outcome is particularly interesting for patients with CD.[28] Please see our outcome section for a full description of all our outcomes of interest.	5

Outcomes of Interest

Primary outcome

Change in objective measures of Crohn's severity (Measured by CDAI or CDEIS)

Justification: The CDAI is a score based on eight variables that determine disease activity: number of stools, abdominal pain, general well-being, extraintestinal complications, antidiarrheal agents used in the previous seven days, abdominal mass felt on palpation, hematocrit, and body weight.[12] The CDEIS is a score the uses endoscopic assessments to determine disease activity.[52,53] These are the most common measure of CD treatment success because it is directly correlated to improved CD-related symptoms.[52,53] Because severity is related to symptom improvements and a better quality of life, this outcome is particularly interesting for patients with CD.[28]

Secondary outcomes

Benefits

Change in subjective measures of Crohn's severity (Measured in self-reported pain and quality of life)

Justification: Both treatments aim to reduce CD related symptoms, like pain and quality of life.[5,29] Abdominal pain is a common symptom of CD, so it is a standard measure of success if the pain has decreased from baseline.[29] In addition, pain is a disabling and difficult magnification of CD that can lead to decreased quality of life, so a decrease in pain is a clinical outcome of relevance.[29]

Change in inflammation (Plasma levels of C-reactive protein, tumor necrosis factor, interleukin expression, erythrocyte sedimentation rate, α1-acid glycoprotein, mucosal inflammation, inflammatory mrna expression)

Justification: Increased inflammation is associated with CD. Inflammation can be measured through a variety of means, including inflammatory biomarkers found in serum, fecal matter, and tissue samples of patients.[30,31] These biomarkers often indicate the severity of symptoms for patients with CD. Another sign of inflammation is leakage in the tight junctions.[32,33] Reduced tight junction expression is positively correlated with Crohn's Disease symptom severity.[22]

Harms

Side effects of herbal therapy (Counts of adverse events)

Allergic reactions, rashes, asthma, headaches, dizziness, agitation, dry mouth, seizures, fatigue, tachycardia, nausea, vomiting, and diarrhea.[54]

Change in liver function (Measured in blood tests)

Justification: Atotoxicity (liver damage) is a possible effect of herbal therapy. It is rare and only occurs in susceptible individuals; however, it is a possible harmful outcome due to this type of TCM.[54,55]

Side effects of TwHF (Counts of adverse events)

Some possible side effects of TwHF include gastrointestinal discomfort, similar symptoms as general herbal therapy; however, rate of severe side effects is low.[56]

Side effects of Moxibustion (Counts of adverse events)

Possible burning of skin during application, similar symptoms as general herbal therapy; however, it is not safe for pregnant individuals. It could possibly lead to basal cell carcinoma or skin cancer, but this is extremely rare and not much knowledge exits on this matter.[57]

Side effects of Fufangkushen colon-coated capsule (Counts of adverse events)

No severe effects are known, similar symptoms as general herbal therapy.[22]

Appendix 3: Search Strategies

Database: MEDLINE via PubMed

Dates covered: 1946 to present. Latest search run: 1/17/2023. Assisted by reference librarian Heather Blunt.

Limits: None

Search terms/results:

Search	Query	Items Found
1	"Medicine, Chinese Traditional"[Mesh] OR "Drugs, Chinese Herbal"[Mesh] OR "Acupuncture therapy"[Mesh] OR "Moxibustion"[Mesh] OR "Cupping therapy"[Mesh] OR "Tripterygium"[Mesh] OR Traditional Chinese Medicine[tiab] OR Acupuncture[tiab] OR Cupping[tiab] OR Moxibustion[tiab] OR TCM[tiab] OR Chinese Herb*[tiab] OR Tripterygium wilfordii Hook[tiab] OR Fufangkushen[tiab] OR Thundergod vine[tiab] OR Leigong teng[tiab] OR fufang kushen[tiab]	123,960
2	“Crohn Disease”[Mesh] OR Crohn*[tiab]	64,260
3	#1 AND #2	131

Database: The Cochrane Library via CENTRAL and CDSR

Dates covered:

CENTRAL: 1898 to present. Latest search run: 1/30/2023. Assisted by reference librarian Heather Blunt.

CDSR: 1996 to present. Latest search run: 1/30/2023. Assisted by reference librarian Heather Blunt.

Limits: None

Search terms/results:

Search	Query	Reviews	Trials	Special Collections
1	"Crohn*"	67	5457	0
2	"Acupuncture*" OR (Chinese NEXT herb*) OR "Traditional Chinese Medicine" OR Moxibustion OR Cupping OR Tripterygium OR Fufangkushen OR Leigongteng OR Fufang kushen OR “Thundergod vine” OR TCM	274	34368	0
4	#1 AND #2	3	44	0

Cochrane Reviews (CDSR): 3
Trials (CENTRAL): 44
Special Collections: 0
Database: Scopus
Dates covered: 1937 to present. Latest search run: 1/30/2023. Assisted by reference librarian Heather Blunt.
Limits: None
Search terms/results:

Search	Query	Results
1	TITLE-ABS-KEY("Crohn*")	93,602
2	TITLE-ABS-KEY("Acupuncture*" OR "Chinese herb*" OR "Traditional Chinese Medicine" OR Moxibustion OR Cupping OR Tripterygium OR Fufangkushen OR “Thundergod vine” OR TCM OR “fufang kushen” OR “Leigong teng”)	159,580
4	#1 AND #2	263

Database: CINAHL
Dates covered: 1937 to present. Latest search run: 1/30/2023. Assisted by reference librarian Heather Blunt.
Limits: None
Search terms/results:

Search	Query	Reviews
1	"Crohn*" OR (MH "Inflammatory Bowel Diseases+") OR (MH "Crohn Disease") OR (MH "Ileitis+")	21,167
2	"Acupuncture*" OR "Chinese herb*" OR "Traditional Chinese Medicine" OR Moxibustion OR Cupping OR Tripterygium OR Fufangkushen OR Leigongteng OR Fufang kushen	42,935
4	#1 AND #2	350

TRIAL REGISTRY SEARCHES

Database: ClinicalTrials.gov
Dates covered: 1997 to present. Latest search run: 1/17/2023. Assisted by reference librarian Heather Blunt.
Limits: None
Search terms: We will search this site using the term "Crohn Disease" as a condition and the terms “Traditional Chinese Medicine OR Acupuncture OR cupping OR moxibustion” as interventions.
Results: 7 overall "hits", 3 completed studies, 4 ongoing studies.

OTHER SEARCHES

Source: Google Scholar
Dates covered: 1995 to present. Assisted by reference librarian Heather Blunt.
Date of search: Latest search run: 1/17/2023.
Limits: None

Search terms: We will search Google Scholar by typing ("Crohn's disease" OR "Crohn") AND ("Traditional Chinese" OR "acupuncture" OR "moxibustion" OR "chinese herb" OR "Cupping" OR "Tripterygium" OR "Fufangkushen" AND ("placebo" OR "sham") AND (randomized) in the search box with “articles” and “including patients” checked.
Results: This yielded 4,660 results. We plan to scan the first 25 pages of results, but will continue further if necessary until two consecutive pages contain no relevant articles.

EXPERT CONTACT

Expert: Dr. Corey Siegel MS, MD
Title/affiliation: Section Chief, Gastroenterology and Hepatology at Dartmouth-Hitchcock; Professor of Medicine, Geisel School of Medicine
Date of contact: December 2022
Results: Partnership initiated

Appendix 4: Data Collection Form[23]

List of variables included in Data Collection Form:

1. Researcher Initials
2. Source
3. Title
4. Author(s)
5. Publication year
6. Country
7. Study design
8. Study aims
9. Setting
10. Medical condition/field associated with study
11. Participant demographics
    a. Mean age (in years)
    b. Gender (%/n, M/F/Other)
    c. Race
12. Number of participants enrolled at baseline (n)
    a. Total
    b. Intervention
    c. Control
13. Outcome measure: Objective Change in measures of Crohn's severity (CDAI Score)
    a. Measurement tool or method used
    b. Result summary
    c. When measured (post-treatment)
    d. Intervention mean (SD) or 95% CI or SE
    e. Control mean (SD) or 95% CI or SE
    f. When measured (follow-up)
    g. Intervention mean (SD) or 95% CI or SE
    h. Control mean (SD) or 95% CI or SE
14. Outcome measure: Objective Change in measures of Crohn's severity (CDEIS Score)
    a. Measurement tool or method used
    b. Result summary
    c. When measured (post-treatment)
    d. Intervention mean (SD) or 95% CI or SE
    e. Control mean (SD) or 95% CI or SE
    f. When measured (follow-up)
    g. Intervention mean (SD) or 95% CI or SE
    h. Control mean (SD) or 95% CI or SE
15. Outcome measure: Subjective measure of Crohn’s severity
    a. Measurement tool or method used
    b. Result summary
    c. When measured (post-treatment)
    d. Intervention mean (SD) or 95% CI or SE
    e. Control mean (SD) or 95% CI or SE
    f. When measured (follow-up)
    g. Intervention mean (SD) or 95% CI or SE
    h. Control mean (SD) or 95% CI or SE
16. Outcome measure: Change in Inflammation (Plasma levels of CRP, TNF, IL, erythrocyte sedimentation rate, α1-acid glycoprotein, mucosal inflammation, inflammatory mrna expression)
    a. Measurement tool or method used

    b. Result summary
    c. When measured (post-treatment)
    d. Intervention mean (SD) or 95% CI or SE
    e. Control mean (SD) or 95% CI or SE
17. Intervention(s) characteristics
    a. Brief Name (name or phrase that describes the intervention)
    b. Description of intervention
    c. Length of intervention
    d. Mode of delivery
    e. When was the intervention delivered?
    f. Where did the intervention occur?
    g. Who provided the intervention?
    h. How many times was the intervention delivered?
18. Control characteristics
    a. Description
    b. Duration of control
19. Follow-up
    a. Duration for both intervention and control (note if different)

Appendix 5: Methodological Quality Assessment Tool[23]

- Domain 1: Risk of bias from the randomization process
  - Random allocation sequence?
  - Concealed allocation sequence?
  - Did baseline differences between intervention groups suggest a problem with the randomization process?
- Domain 2: Risk of bias due to deviations from the intended interventions
  - Were participants blinded to their assigned intervention?
  - Were the people who applied the intervention blinded to participants' assignments?
- Domain 3: Missing outcome data
  - Were data for this outcome available for all, or nearly all, participants randomized?
  - Is there evidence that the result was not biased by missing outcome data?
  - Could missingness in the outcome depend on its true value?
  - Is it likely that missingness in the outcome depended on its true value?
- Domain 4: Risk of bias in measurement of the outcome
  - Was the method of measuring the outcome inappropriate?
  - Could measurement or ascertainment of the outcome have differed between intervention groups?
  - Were outcome assessors aware of the intervention received by study participants
  - Could assessment of the outcome have been influenced by knowledge of intervention received?
  - Is it likely that assessment of the outcome was influenced by knowledge of intervention received?
- Domain 5: Risk of bias in selection of the reported result
  - Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?
  - Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?
  - Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?
- Overall Bias (Rated Low, Medium, or High)

Appendix 6. General Study Characteristics of Excluded Studies

Authors (Year Published)	**Location**	**Study Design**	**Participants**	**Control**	**Interventions**	**Reason for Exclusion**
Ren J, Tao Q, Wang X, Wang Z, Li J (2007)[36]	China	Prospective Study	16 patients with active CD	None	T2: a chloroform/ methanol extract of TWHF	Prospective Study without control group

Bao C, Liu P, Liu H, et al. (2016)[39]	China	Prospective Cohort	34 participants with CD and 36 healthy controls (n=70)	Right-handed, healthy individuals (n=36)	Electro-acupuncture (n=16) or moxibustion treatment (n=18)	Prospective Study without control group
Bao C, Wu L, Wu H, et al. (2016)[35]	China	RCT	95 patients with mild to moderate CD	Wheat-bran-partitioned moxibustion combined with superficial needle puncture at non-meridian, non-acupoint sites (n=48)	Herb-partitioned moxibustion combined with acupuncture (n= 47)	TCM measurements of subjective measures of IBD symptoms
Bao C, Liu H, Shi Y et al. (2018)[37]	China	RCT	47 patients with CDAI greater than 150	Sham moxibustion and sham acupuncture (n=21)	Mild warm moxibustion combined with acupuncture (n=26)	No full text
Matsuno Y, Hirano A, Torisu T et al. (2019)[38]	Japan	RCT	8 patients with CD	N/A	Indigo naturalis	Retrospective Cohort Study
Abbreviations: CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index ; RCT,						

Randomized controlled trial; TWHF, Tripterygium wilfordii Hook F; TCM, Traditional Chinese medicine; IBD, Inflammatory bowel disease

Appendix 7. TCM Interventions Utilized in Included Studies[28]

Authors (Year Published)	Intervention	Duration of Intervention	Total Number of Treatments	Notes Concerning Intervention
Bao CH, Zhao JM, Liu HR (2014)[18]	Herb-partitioned moxibustion combined with acupuncture	12 weeks	36 sessions	Acupoints were selected based on TCM principles according to the clinical manifestations of the patients. Herbal cake recipe used for moxibustion in the treatment group included Coptis chinensis, Radix Aconiti Lateralis, Cortex Cinnamomi, Radix Aucklandiae, Flos Carthami, Salvia miltiorrhiza, and Angelica sinensis as the main ingredients. Herb-partitioned moxibustion and acupuncture were performed at the same time once every other day (three times per week) for a total of 36 sessions (12 weeks). Subjects who received at least 80% of the required number of treatment sessions (29 or more) were considered to have completed the entire treatment plan.
Joos S,	Acupuncture	4 weeks	10 sessions	Patients were treated in the sitting

Brinkhaus B, Maluche C, Maupai N, Kohnen R, Kraehmer N, Hahn EG, Schuppan D (2014)[31]	and moxibustion			position at the back points for 10 min. After removing the back needles patients were treated at acupuncture points on the front for 20 min while lying on their backs. All needles were inserted between 0.5 and 3 cm and manipulated by hand at the beginning, in the middle and at the end of each treatment until the patient felt an aching, dull or tingling sensation, known as 'de-qi' in TCM. Depending on the Chinese diagnosis, patients of the TCM group were treated with moxa burned down in a wooden box positioned on the abdomen. All patients were reevaluated after 5 acupuncture sessions and, in case they presented with changes in symptoms, tongue or pulse, individual acupoints were exchanged.
Zhao C, Bao C, Li J, et al. (2015)[32]	Herb-partitioned moxibustion combined with acupuncture	12 weeks	36 sessions	Moxibustion was performed on the Tianshu (ST25, bilateral), Qihai (CV6), and Zhongwan (CV12) acupoints; and acupuncture was performed at the Zusanli (ST36), Shangjuxu (ST37), Sanyinjiao (SP6), Taixi (KI3), Gongsun (SP4), and Taichong (LR3) acupoints.

				Herbal cake recipe used for moxibustion in the treatment group included Coptis chinensis, Radix Aconiti Lateralis, Cortex Cinnamomi, Radix Aucklandiae, Flos Carthami, Salvia miltiorrhiza, and Angelica sinensis as the main ingredients. Herb-partitioned moxibustion and acupuncture were performed at the same time once every other day (three times per week) for a total of 36 sessions (12 weeks) for 30 minute periods.
Guo S, Zhou J, Zhang L, et al. (2022)[33]	Patients received moxibustion controlled at 43 ℃ combined with acupuncture	12 Weeks	36 sessions	The patient received treatment according to the grouping in a room at 26±1 ℃. In the observation group, patients received moxibustion controlled at 43 ℃ combined with acupuncture.
Bao C, Wu L, Wang D. (2022)[34]	Acupuncture and moxibustion	12 weeks	36 sessions	Acupoints that were selected include Zhongwan (CV12) and bilateral Shangjuxu (ST37), Sanyinjiao (SP6), Gongsun (SP4), Taichong (LR3), Taixi (KI3), Hegu (LI4), and Quchi (LI11)17 according to the World Health Organization standard. Single-use 0.30 × 40 mm or 0.30 × 25 mm acupuncture needles (Hwato,

				Suzhou, China) 30,31 were vertically inserted into each acupoint to 20–30 mm depth to obtain a deqi sensation (a soreness, distention, numbness or heaviness sensation). Bilateral Zusanli (ST36) and Tianshu (ST25) were selected for moxibustion. Pure moxa sticks (diameter: 2·8 cm; Hanyi, Nanyang, China) were ignited and fixed on a moxibustion stand at a distance of 3–5 cm to the surface of acupoints. The temperature of skin surface at the acupoints was maintained at 43 ± 1 °C and monitored with a miniature infrared thermometer (Fluke 62, Fluke Corporation, Everett, WA, USA). Acupuncture and moxibustion were concomitantly performed for 30 min.
Abbreviations: TCM, Traditional Chinese Medicine				

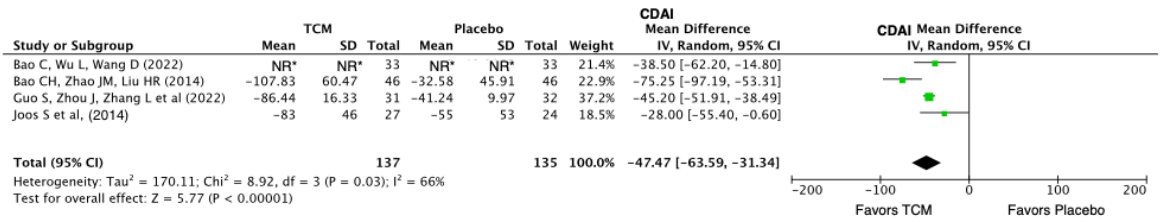
Appendix 8. Results for Primary Outcome: CDAI and CDEIS Scores of Post-Treatment Measurements with Intervention and Control Mean Difference

Authors (Year Published)	**Measurement Tool or Method Used**	**When Measured (Post-Treatment)**	**Intervention Mean Difference (Mean ± SD)**	**Control Mean Difference (Mean ± SD)**	**Difference in mean CDAI/CDEIS decreases (Mean ± SD)**
Bao CH,	CDAI	12 weeks	-107.83 ±	-32.58 ±	75.25 ± 11.19

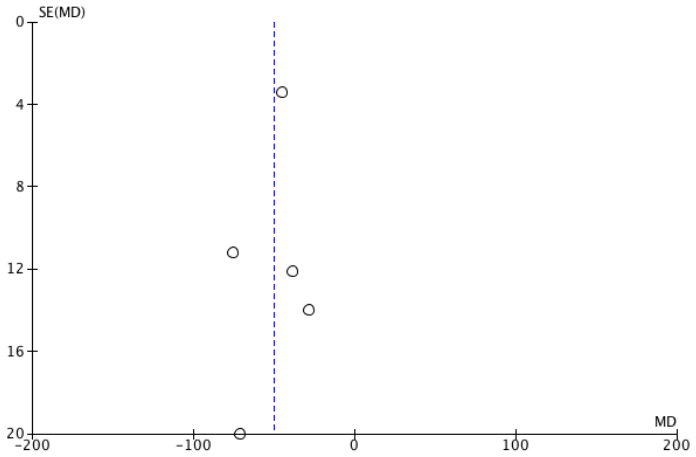
Zhao JM, Liu HR (2014)[18]			60.47	45.91	
Joos S, Brinkhaus B, Maluche C, Maupai N, Kohnen R, Kraehmer N, Hahn EG, Schuppan D (2014)[31]	CDAI	12 weeks	-83 ± 46	-55 ± 53	28 ± 13.98
Zhao C, Bao C, Li J, et al. (2015)[32]	CDAI	12 weeks	-111.15 ± 54.74	-40.51 ± 31.36	70.64 ± 19.95
Guo S, Zhou J, Zhang L, et al. (2022)[33]	CDAI	12 weeks	-86.44 ± 16.33*	-41.24 ± 9.97*	45.2 ± 3.42
Bao C, Wu L, Wang D. (2022)[34]	CDAI	12 weeks	Not reported	Not reported	-38.5 ± 12.09
Bao CH, Zhao JM, Liu HR (2014)[18]	CDEIS	12 weeks	-2.28 ± 5.52	-0.60 ± 4.75	-1.68 ± 2.18
Bao C, Wu L, Wang D. (2022)[34]	CDEIS	48 weeks	-7.3 ± 1.79	-2.0 ± 1.38	-5.25 ± 2.18

Abbreviations: CD, Crohn's Disease; CDAI, CDEIS, Crohn's Disease Activity Index; SD, Standard Deviation

***Calculated through WebPlotDigitizer because raw data was not available.**



Appendix 9. **Forest plot for sensitivity analysis of data extraction from WebPlotDigitizer** [29]



Appendix 10. A funnel plot of the included studies on CDAI outcome. Included studies demonstrate no evident risk of publication bias for the random-effects model on CDAI.