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USE OF IMMPACT DOMAINS IN CLINICAL TRIALS OF ACUPUNCTURE FOR CHRONIC PAIN: A PROTOCOL FOR A METHODOLOGICAL SURVEY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014904
Article Type:	Protocol
Date Submitted by the Author:	25-Oct-2016
Complete List of Authors:	Mazzei, Lauren; Universidade de Sorocaba, Programa de Pós-Graduação em Ciências Farmacêuticas Bergamaschi, Cristiane; University of Sorocaba, Pharmaceutical Science Silva, Marcus; Federal University of Amazonas, Clinical Epidemiology Lopes, Luciane; UNISO, Pharmacie Science
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Complementary medicine, Evidence based practice
Keywords:	Acupuncture, Chronic Pain, Methodological Survey

USE OF IMMPACT DOMAINS IN CLINICAL TRIALS OF ACUPUNCTURE FOR CHRONIC PAIN: A PROTOCOL FOR A METHODOLOGICAL SURVEY

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2577 words

SUMMARY

INTRODUCTION: Pain is one of the most common and most debilitating complaints among patients. They affect the individual, their relationship with friends and family, their work force, and their sociability. Acupuncture is one of the therapeutic resources for managing chronic pain. Given the variability of outcome measures in Controlled Randomized Clinical Trials on Non-Oncologic Chronic Pain (CRCT-NOCP), the Initiative in Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) recommends six domains to be covered in evaluating the effectiveness of treatments for chronic pain.

OBJECTIVE: The main objective of this study is to check whether researchers have used IMMPACT recommendations in measuring CRCT-NOCP outcomes when acupuncture was used as a treatment.

METHOD: This is a methodological study. We will systematically search for eligible studies in specific database with a defined strategy. We are to use terms of MeSH "acupuncture", "chronic pain" and its similar terms, without idiom restrictions. Eligible studies include those which randomized and chose NOCP patients to be treated with acupuncture or control (sham acupuncture or no acupuncture), recruited after September 2004, number of patients equal or less than 100. The measured outcomes are to be the presence of outcome domains recommended by IMMPACT, domains reported by patient or clinician, tools used to measure such domains, besides other features of the studies. We shall conduct a regression analysis to explore factors which can be associated with the presence of outcome domains according to IMMPACT recommendations.

ETHICS AND DISSEMINATION: This survey will be submitted to presentation in congresses and publishing in a scientific journal. The evidence obtained in this study will allow us to measure the quality of the evidence and greater transparency in decisions regarding the use of acupuncture as a viable alternative to managing chronic pain.

Keywords: Acupuncture. Chronic Pain. Methodological Survey.

Strong Points and Limitations of this Study

- ✓ This is the first study to evaluate the outcome domains used in CRCT using acupuncture as intervention to the treatment of NOCP.
- ✓ Acupuncture can be an effective therapy in chronic pain control, avoiding costly expenses with analgesic medication which generate dependence (opioids), or limiting adverse effects as in the case of non-steroid anti-inflammatories (gastric ulcer and

cardiovascular events) that have a direct impact in the patient's life. Therefore, checking compliance with IMMPACT recommendations in CRCT about NOCP may appraise the quality of the evidence and provide greater transparency in decisions regarding the use of acupuncture as a viable alternative in this clinical condition. It can also guide physicians in clinical practice decision making.

- ✓ The methods contain explicit eligibility criteria, a comprehensive research and a double independent selection, including independent appraisal of bias risk.
- ✓ Primary studies are probably limited in conception and outcome measures and thus, they have high bias risk. Besides, techniques or point categories used in acupuncture may be uncertain or varied in different studies.
- ✓ This enquiry has not received any specific sponsorship from any public, private or non-profit agency.

INTRODUCTION

Non-Oncologic Chronic Pain (NOCP) is defined as a persisting painful feeling for more than some months, which may be associated to traumas and illnesses [1] or not. It is estimated that 18,9% of the world population present chronic pain. It is one of the most common complaints among patients, affecting not only the subject in their individuality, but also in a general way [2].

It is regarded as a health problem that consumes 22% of primary health appointments on average. In the United States, costs with pain medication are around US$17,8 billion a year [3}. The Canadian project STOP-PAIN published the average cost of $ 1,462 per individual monthly with chronic pain on waiting lists for multidisciplinary pain treatment facilities. [4]A recent population-based study with a subsample of 562 individuals out of a total of 5,094 Portuguese adults with chronic pain identified a cost of € 1,883.30 per indivudual, totalling €4,611.69 million in the country in 2010 [5].

Despite research efforts to understand molecular biology and nociceptive transmission pathways related to pain resulting in significant advances in pain treatment and better quality of life for patients, the efficacy assessment of certain therapies for managing such condition is below standard [1].

Acupuncture is one of the resources that compose the National Policy of Integrated and Supplementary Practices (NPISP) IN Brazil. It is a possible therapy in managing chronic

pain with sensitive cost reduction to the government and adverse effect reduction to the patient [7]. However, we still find unprepared managers for implementing this policy in the public health system in Brazil nowadays (SUS) [8].

In such scenario, the World Health Organization (WHO) has launched a strategy for the period 2014-2023 to integrate to traditional medicine and supplement the health system in a safe, respectful, accessible and effective way. The aim of the document was to pinpoint challenges in the implementation, present possible strategies to solve them and stimulate the design of serious policies. The base references for elaborating the document are mainly guidelines and strategies developed by the organization [9].

The search for international guidelines approaching the use of acupuncture for NOCP in the adult population results in few findings or in conflicting recommendations. Acupuncture is recommended as an adjunct to conventional treatment of NOCP, but only the American guidelines specify the moment in which it should be used within the conventional drug treatment flow [2 10-12].

Among the policies we looked up, the recommendation of acupuncture for many painful conditions is based on low quality evidence due to the diversity in the methodology of CRCT [2 10-12]. Besides this, such guidelines do not discriminate the power of the recommendation, except for those in Scotland and Canada [2 12].

A systematic review of thirteen CRCT assessed the analgesic effects of acupuncture as compared to sham acupuncture in adult patients with chronic pain in conditions of knee osteoarthritis, tension headache, migraine, low back pain, fibromyalgia, abdominal pain in scar, postoperative and procedural pain due to colonoscopy. The outcomes showed analgesic effect without clinical relevance, in favor of acupuncture [13].

Even showing quality, CRCT with adequate randomization and blinding may not provide the best approach for the development of strong evidence base for managing pain, in case the outcomes and its tools are not adequate [14]. Such limitations have been recognized internationally, leading to the development of the Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) in 2002.

The initiative gathered 27 experts from universities, governmental agencies and pharmaceutical industry, who identified consensually a nucleus of six outcome domains that should be considered in CRCT for chronic pain [15]. The outcome domains considered were: (1) pain; (2) physical function; (3) emotional state; (4) evaluation of the participants regarding improvement and satisfaction with treatment; (5) adverse symptoms; and (6) the participant's willingness [16].

The establishment of a standard set of outcome domains in CRCT about chronic pain encourages researchers to consider chronic pain as a complex phenomenon which affects patients in multiple dimensions. It protects against the polarization of selective outcomes, a common problem in all medical literature. It makes systematic reviews and Meta analyses easier, which allows researchers to generate more precise estimations of treatment effects due to sharing common outcomes of individual trials [17].

Variability in outcome measures in CRCT about NOCP generates inaccuracies in the effectiveness of certain treatments. Although the recommendation of IMMPACT was published in 2003 and updated in 2008, there is no information on whether subsequent clinical trials published comply with IMMPACT recommendations on their outcome measures.

The general aim of this project is to verify changes occurred in the way of reporting and assessing outcomes after the publication of IMMPACT recommendations in CRCT about the use of acupuncture in patients with NOCP.

METHODS

Study Design

The study comprises a methodological survey of randomized clinical trials which used acupuncture for the treatment of chronic pain [18]. The methodological survey is a type of study on method enquiry, with data collection form selected CRCT, not based on questionnaires but using systematic methods in its execution.

Reference Sources and Search

All trials to be included are CRCT-NOCP selected in the systematic review carried out by Vickers et al. [18]. Trials comply with the latest review published on the theme, where authors carried out meta-analysis of individual data. Additional research is to be performed in studies dating as from June 2010 and 6 months before the systematic review of the comprehensive search date on the theme (considering delay in indexing). The search for eligible studies will be accomplished by systematic research of database, namely Lilacs, CINAHL, EMBASE, MEDLINE, AMED, Web of Science, Clinical Trials and Cochrane Central Registry of Controlled Trials, with a defined search strategy, free of idiom restriction.

We shall combine the main terms “Chronic Pain” and “Acupuncture” indexed in the MeSH system,. Firstly, we will search the isolate terms and their synonyms, and then we will make a second search, combining and crossing the terms. Appendix A, Table 1.

We will verify the reference or citation list found in secondary studies to identify possibly eligible studies. When necessary, we shall contact the authors of the main studies to obtain further information.

Study Elligibility Criteria

Design:: controlled randomized clinical trials, whose patient recruitment occurred from September 2004 (for the six domains) to March 2009 (for the four domains) and whose number of patients is equal or more than 100.

Clinical condition:: studies which include patients aged 18 or older, with non-oncologic chronic pain. Eligible pain conditions: non-oncologic chronic pain, whose episode should have lasted at least four weeks.

Intervention:: the studies should include a group of patients treated with acupuncture, and another group where patients were treated with sham acupuncture or no acupuncture, and studies where the choice blinding is unmistakable and adequate.

Exclusion Criteria: The following trials are to be excluded: neck pains associated with specific clinical conditions (e.g, fractures resulting from ostheoporosis), shoulder pains associated with specific clinical conditions (Rotator cuff tendinitis, frozen shoulder, or bursitis).

Determination of Eligibility

Two reviewers, in pairs, will evaluate independently whether summaries and titles are according to the eligibility criteria. Differences are to be solved by consensus among all reviewers. To assess the agreement of the selection we will use Kappa Test, given that kappa values between 0,40 and 0,59 are to be considered weak agreement, between 0,60 and 0,74 medium agreement, and 0,75 or more excellent agreement.

In order to exclude doubled articles, one reviewer will analyze all the eligible articles and identify those which have one or more authors in common. In case of doubled publication, we will use the article with most complete data.

Data Extraction

We will adopt an Excel spreadsheet for the abstraction of data, to be used by two reviewers separately. A third reviewer will check the Excel spreadsheet to ensure the coherence of the answers obtained among collaborators and use the consensus when necessary.

For articles published only in summary or for those with important information missing, we will look for complete information about methods and results by contacting the authors.

Two reviewers will be calibrated by the extraction of at least three articles and next, will perform the consensus, in pairs and independently. This procedure shall occur until reviewers are able to extract the data. The collected data will be: name of the first author, date of publication, country of origin, impact of the journal, recruitment date of the first participant, presence of outcome domains IMMPACT, and the tools used for measuring the outcome domains, method of acupuncture, type of patient, duration of treatment. Besides this, the study will check if fundamental outcomes are reported by the patient (ORP), if clinical outcomes are reported (COR), if the outcome was reported by a third person (ORT), or a combination of the items above.

The data will be recorded to be transferred to a statistical analysis program later. A regression analysis will be conducted to explore factors that may be associated with the presence of outcome domains according to IMMPACT recommendations.

Risk of Bias

A modified version of Cochrane for risk of bias will be used [17]. Reviewers will evaluate the risk of bias for each randomized trial independently, according to the following criteria: generation of random sequence, hiding of the choices, blinding of participants and professionals, blinding of outcome evaluators, if outcomes were reported adequately; incomplete outcomes; selective outcome reporting and other sources of bias. Reviewers will attribute answer alternatives “definitely yes”, “probably yes”, “probably not” and “definitely not” for each of the domains. Ultimately, “definitely yes” and “probably yes” will be attributed low risk of bias, whereas “definitely not” and “probably not” mean high risk of bias. Reviewers will solve divergences through discussion, and a third person will judge unsolved divergences.

Definitions of IMMPACT outcome domain

The six IMMPACT domains recommended in 2003 which will be captured in this study are listed below, together with their definitions

1. Pain: Includes various aspects of pain evaluation (e.g, intensity of pain, duration and frequency). The global evaluation of pain is a general assessment which examines how the pain changed during the treatment.

2. Physical function: refers to the participant's capacity to conduct their daily activities (e.g, tasks, walks, trips and self-care), strength and resistance.

3. Emotional state: refers to the treatment associated to emotional anguish (e.g, depression, anxiety, anger or irritability).

4. Patient's classification of improvement and satisfaction with the treatment: refers to the participant's feeling with the treatment (that is, if they feel the positive features of the treatment surpass the negative ones). This domain overcomes pain classification only.

5. Adverse symptoms and effects: refers to side effects caused by the treatment. The symptoms should be evaluated at the beginning of the trial, followed by the evaluation of symptoms and adverse events that come up during the study. Such measures may be taken in terms of presence, change and importance for the participants.

6. Willingness and participation: includes information about the participant's joining or withdrawing the treatment regime.

Trials with patients' recruitment as from March 2009 can only report the four first domains, according to the new recommendations of IMMPACT published in 2008.

Statistical Analysis

The authors will summarize data by using mean and standard deviation (SD) for continuous variables in normal distribution; median and interquartile range (IQR) for continuous variable which were not in a normal distribution; and proportions for categorical variables. We will perform logistic regression adjusted to analysis and hypothesis. The associations with the highest IMMPACT domain rates are: (1) The latest published trials, (2) Trials published in the strongest impact journals, and (3) Trials that started recruiting participants a year after the publication of IMMPACT recommendations. We will estimate the date when recruitment started for trials whose recruitment start are not reported as the average duration from the beginning of the recruitment period to the publication date for trials which reported such information. We are to carry out logistic regressions adjusted to the analysis and

hypothesis. The associations with the biggest IMMPACT domains are: (1) the latest published trials, (2) trials published in the strongest impact journals, and (3) trials which started recruiting participants one year after the publication of IMMPACT recommendations. For trials with unreported recruitment dates, we will use an estimation based on information from adequately reported trials, that is, the mean of beginning of recruitment, number of sessions and publication dates.

A model per IMMPACT domain that shows enough variability in the report is to be considered adequate: stricktly speaking, we shall not consider domains reported in less than 10% or more than 90% of the total number of outcomes assessed in all the clinical trials. Multicollinearity tests will examine whether any predictors were correlational. Specifically, we will calculate inflation rates of the variance associated with each independent variable in each regression model, and we will consider values that may indicate the presence of multicollinearity. In case multicollinearity between two variables is detected, we shall remove the variable(s) of minor importance. We will calculate odds ratios and associations of confidence intervals of 95% (IC), with the definition of significance level of $P < 0,05$ for all the analyses.

The authors are to carry out all the statistical analyses by using STATA , version 14.1.

DISCUSSION

Our survey will evaluate methodologically the outcomes of CRTC which used acupuncture for NOCP. It will provide efficacy estimations for treatments, and assess the quality of evidence in a thorough and consistent way by using recommendations provided by IMMPACT. Our survey's outcomes will be significant for public health and for health professionals all over the world, mainly in Brazil.

Since the publication of IMMPACT, it is not known whether studies using acupuncture as an intervention for chronic pain follow IMMPACT's recommendations. Without consistent and more thorough standard outcome reports for patients in CRTC and NOCP, the authors of such studies will be unable to judge objectively the effects of acupuncture. The data compiled on the use of acupuncture will inform both patients and health professionals about its efficacy and safety. Therefore, multiprofessional care and decision making based on evidence will be made easier.

This Project aims at exploring some hypotheses to determine the use of IMMPACT recommendations on CRTC–NOCP. After the publication of IMMPACT orientations in August 2003 and later, in 2008, CRTC–NOCP which started recruiting participants as from September 2004 had better reports of main outcomes, regarding IMMPACT domains versus journals with lower impact factors. The main domains were reported by the patient, by the clinician, by a third person or by a combination of these subjects.

ETHICS AND DIFUSION

Ethics is not necessary, as this is protocol for a methodological survey. The survey will be published in a jornal and presented in congresses with reviews by peers. The evidence of this study will allow health professionals to verify the efficacy and safety of acupuncture for the treatment of NOCP. Updates of this study should be conducted to inform and orient the practice of health care.

Contributors: LCL is the main researcher who leaded the writing of the manuscript. CCB and LGM are the project manager, co-researcher, who contributed to and writing and review of the manuscript. MTS is co-researcher, and contributed to the writing and review of the manuscript. All the authors have read and approved of the final manuscript.

Acknowledgments: The authors thank Dr. Caio Guimarães for his expert advice.

Sponsorship: This Project has not received any specific funding of any public, private or non-profit agency.

Interest conflict: None.

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Table 1. Search Strategy for database

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 exp Acupuncture Analgesia/
2 exp Acupuncture/
3 acupuncture.mp.
4 1 OR 2 OR 3
5 chronic pain.mp.
6 exp Chronic Pain/
7 exp Chronic Disease/
8 5 OR 6 OR 7
9 4 AND 8

Database: Embase <1974 to 2016 June 28>
Search Strategy:
1 exp acupuncture analgesia/
2 acupuncture.mp.
3 exp acupuncture/
4 1 OR 2 OR 3
5 exp chronic pain/
6 chronic pain.mp.
7 5 OR 6
8 4 AND 7

Database: AMED (Allied and Complementary Medicine) <1985 to June 2016>
Search Strategy:
1 acupuncture.mp.
2 exp Acupuncture/
3 1 OR 2
4 exp Chronic disease/
5 chronic pain.mp.
6 4 OR 5
7 3 AND 6

Database: CINAHL
Search Strategy:
1 (MH "Acupuncture+")
2 (MH "Acupuncture Analgesia")
3 1 OR 2
4 (MH "Chronic Pain")
5 3 AND 4

Database: Cochrane Library
Search Strategy:
1 "acupuncture":ti,ab,kw
2 "acupuncture analgesia":ti,ab,kw
3 1 OR 2
4 "chronic pain":ti,ab,kw
5 3 AND 4

Database: Web of Science <1976 to July 2016>
Search Strategy:
1 acupuncture

2 *acupuncture*
3 1 OR 2
4 chronic pain
5 chronic *pain*
6 4 OR 5
7 3 AND 6

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract			not applicable
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		☐	not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		10
Sponsor	5b	Provide name for the review funder and/or sponsor		☐	not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		☐	not applicable
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐		5

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		5, 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		5, 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐		5, 6
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐		7
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		8, 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐		8, 9
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐		9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		9

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		7, 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		☐	not applicable

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014904.R1
Article Type:	Protocol
Date Submitted by the Author:	19-May-2017
Complete List of Authors:	Mazzei, Lauren; Universidade de Sorocaba, Programa de Pós-Graduação em Ciências Farmacêuticas Bergamaschi, Cristiane; University of Sorocaba, Pharmaceutical Science Silva, Marcus; Federal University of Amazonas, Clinical Epidemiology Lopes, Luciane; UNISO, Pharmacie Science
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Complementary medicine, Evidence based practice
Keywords:	Acupuncture, Chronic Pain, Methodological Survey

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2305 words

SUMMARY

INTRODUCTION: Pain is one of the most common and most debilitating complaints among patients. They affect the individual, their relationship with friends and family, their work force, and their sociability. Acupuncture is one of the therapeutic resources for managing chronic pain. Given the variability of outcome measures in Controlled Randomized Clinical Trials on Non-Oncologic Chronic Pain (CRCT-NOCP), the Initiative in Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) recommends six domains to be covered in evaluating the effectiveness of treatments for chronic pain.

OBJECTIVE: The main objective of this study is to check whether methodological quality of outcome reporting in published trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes when acupuncture was used as a treatment.

METHOD: This is a methodological study. We will systematically search for eligible studies in specific database with a defined strategy. We are to use terms of MeSH "acupuncture", "chronic pain" and its similar terms, without idiom restrictions. Eligible studies include those which randomized and chose NOCP patients to be treated with acupuncture or control (sham acupuncture or no acupuncture), recruited after September 2004, number of patients equal or more than 100. The measured outcomes are to be the presence of outcome domains recommended by IMMPACT, domains reported by patient or clinician, tools used to measure such domains, besides other features of the studies. We shall conduct a regression analysis to explore factors which can be associated with the presence of outcome domains according to IMMPACT recommendations.

ETHICS AND DISSEMINATION: This survey will be submitted to presentation in congresses and publishing in a scientific journal. The evidence obtained in this study will allow us to measure the quality of the evidence and greater transparency in decisions regarding the use of acupuncture as a viable alternative to managing chronic pain.

Keywords: Acupuncture. Chronic Pain. Methodological Survey.

Strong Points and Limitations of this Study

- ✓ This is the first study to evaluate the outcome domains used in CRCT using acupuncture as intervention to the treatment of NOCP.

- ✓ Acupuncture can be an effective therapy in chronic pain control, avoiding costly expenses with analgesic medication which generate dependence (opioids), or limiting adverse effects as in the case of non-steroid anti-inflammatories (gastric ulcer and cardiovascular events) that have a direct impact in the patient's life. Therefore, checking compliance with IMMPACT recommendations in CRCT about NOCP may appraise the quality of the evidence and provide greater transparency in decisions regarding the use of acupuncture as a viable alternative in this clinical condition. It can also guide physicians in clinical practice decision making.
- ✓ The methods contain explicit eligibility criteria, a comprehensive research and a double independent selection, including independent appraisal of bias risk.
- ✓ Primary studies are probably limited in conception and outcome measures and thus, they have high bias risk. Besides, techniques or point categories used in acupuncture may be uncertain or varied in different studies.
- ✓ This enquiry has not received any specific sponsorship from any public, private or non-profit agency.

INTRODUCTION

Non-Oncologic Chronic Pain (NOCP) is defined as a persisting painful feeling for more than some months, which may be associated to traumas and illnesses or not. [1] It is estimated that 18, 9% of the world population present chronic pain. It is one of the most common complaints among patients, affecting not only the subject in their individuality, but also in a general way. [2]

It is regarded as a health problem that consumes 22% of primary health appointments on average. In the United States, costs with pain medication are around US$17, 8 billion a year. [3] In Canada the average cost is of $ 1,462 per individual monthly with chronic pain on waiting lists [4] and of € 1,883.30 per indivudual, adult in Portugal. [5]

Acupuncture is one of the resources that compose the National Policy of Integrated and Supplementary Practices (NPISP) IN Brazil. It is a possible therapy in managing chronic pain with sensitive cost reduction to the government and adverse effect reduction to the patient. [6] The World Health Organization (WHO) has launched

a strategy for the period 2014-2023 to integrate to traditional medicine and supplement the health system in a safe, respectful, accessible and effective way. [7]

The search for international guidelines approaching the use of acupuncture for NOCP in the adult population results in few findings or in conflicting recommendations. Acupuncture is recommended as an adjunct to conventional treatment of NOCP, but only the American guidelines specify the moment in which it should be used within the conventional drug treatment flow. [8] [9] [10] [2]

Among the policies we looked up, the recommendation of acupuncture for many painful conditions is based on low quality evidence due to the diversity in the methodology of CRCT. [2 8-10] Besides this, such guidelines do not discriminate the power of the recommendation, except for those in Scotland and Canada. [2 8]

Even showing quality, CRCT with adequate randomization and blinding may not provide the best approach for the development of strong evidence base for managing pain, in case the outcomes and its tools are not adequate. [11] Such limitations have been recognized internationally, leading to the development of the Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) in 2002.

The initiative gathered 27 experts from universities, governmental agencies and pharmaceutical industry, who identified consensually a nucleus of six outcome domains that should be considered in CRCT for chronic pain. [12] The outcome domains considered were: (1) pain; (2) physical function; (3) emotional state; (4) evaluation of the participants regarding improvement and satisfaction with treatment; (5) adverse symptoms; and (6) the participant's willingness, but the first four domains listed as main. [13]

The establishment of a standard set of outcome domains in CRCT about chronic pain encourages researchers to consider chronic pain as a complex phenomenon which affects patients in multiple dimensions. It protects against the polarization of selective outcomes, a common problem in all medical literature. It makes systematic reviews and Meta analyses easier, which allows researchers to generate more precise estimations of treatment effects due to sharing common outcomes of individual trials. [14]

Variability in outcome measures in CRCT about NOCP generates inaccuracies in the effectiveness of certain treatments. Although the recommendation of IMMPACT was published in 2003 and updated in 2008, there is no information on whether subsequent clinical trials published comply with IMMPACT recommendations on their outcome measures.

The general aim of this project is to verify changes occurred in the way of reporting and assessing outcomes after the publication of IMMPACT recommendations in CRCT about the use of acupuncture in patients with NOCP.

METHODS

Study Design

The study comprises a methodological survey of randomized clinical trials which used acupuncture for the treatment of chronic pain. The methodological survey is a type of study on method enquiry, with data collection form selected CRCT, not based on questionnaires but using systematic methods in its execution.

Reference Sources and Search

All trials already included in CRCT-NOCP, published as of September 2004, selected in the systematic review carried out by Vickers et al. [15] Additional research will be performed in studies dating as from January 2011 and 6 months before the systematic review of the comprehensive search date on the theme (considering delay in indexing) to nowadays. The search for eligible studies will be accomplished by systematic research of database, namely Lilacs, CINAHL, EMBASE, MEDLINE, AMED, Web of Science, Clinical Trials and Cochrane Central Registry of Controlled Trials, with a defined search strategy, free of idiom restriction.

We shall combine the main terms “Chronic Pain” and “Acupuncture” indexed in the MeSH system. Firstly, we will search the isolate terms and their synonyms, and then we will make a second search, combining and crossing the terms. Appendix A, Table 1.

We will verify the reference or citation list found in secondary studies to identify possibly eligible studies. When necessary, we shall contact the authors of the main studies to obtain further information.

Study Elligibility Criteria

The eligibility criteria for this study will be the same as those adopted in the systematic review published in 2012.

Design: controlled randomized clinical trials, whose patient recruitment occurred from September 2004 and whose number of patients is equal or more than 100.

Clinical condition: studies which include patients aged 18 or older, with non-oncologic chronic pain. Eligible pain conditions: Osteoarthritis, chronic or recurrent headaches, specific and nonspecific shoulder pains, and nonspecific back or neck pain. For osteoarthritis or headaches, it will not be necessary the duration of the pain, since both are of a chronic nature. For pain in the shoulder, back and neck, the pain episode should be at least four weeks in duration.

Intervention: the studies should include a group of patients treated with acupuncture, where acupuncture points or trigger points were stimulated with acupuncture needles, and another group where patients were treated with sham acupuncture or no acupuncture, and studies where the choice blinding is unmistakable and adequate.

Exclusion Criteria: The following trials are to be excluded: neck or back pains associated with specific clinical conditions (e.g., fractures resulting from ostheoporosis).

Determination of Eligibility

Two reviewers, in pairs, will evaluate independently whether summaries and titles are according to the eligibility criteria. Differences are to be solved by consensus among all reviewers. To assess the agreement of the selection we will use Kappa Test, given that kappa values between 0,40 and 0,59 are to be considered weak agreement, between 0,60 and 0,74 medium agreement, and 0,75 or more excellent agreement.

In order to exclude doubled articles, one reviewer will analyze all the eligible articles and identify those which have one or more authors in common. In case of doubled publication, we will use the article with most complete data.

Data Extraction

We will adopt an Excel spreadsheet for the abstraction of data, to be used by two reviewers separately. A third reviewer will check the Excel spreadsheet to ensure the coherence of the answers obtained among collaborators and use the consensus when necessary.

For articles published only in summary or for those with important information missing, we will look for complete information about methods and results by contacting the authors.

Two reviewers will be calibrated by the extraction of at least three articles and next, will perform the consensus, in pairs and independently. This procedure shall occur until reviewers are able to extract the data. The collected data will be: name of the first author, date of publication, country of origin, impact of the journal, recruitment date of the first participant, presence of outcome domains IMMPACT, and the tools used for measuring the outcome domains, method of acupuncture, clinical condition of the patient, duration of treatment. Besides this, the study will check if fundamental outcomes are reported by the patient (ORP), if clinical outcomes are reported (COR), if the outcome was reported by a third person (ORT), or a combination of the items above.

The data will be recorded to be transferred to a statistical analysis program later. A regression analysis will be conducted to explore factors that may be associated with the presence of outcome domains according to IMMPACT recommendations.

Risk of Bias

A modified version of Cochrane for risk of bias will be used. [14] Reviewers will evaluate the risk of bias for each randomized trial independently, according to the following criteria: generation of random sequence, hiding of the choices, blinding of participants and professionals, blinding of outcome evaluators, if outcomes were reported adequately; incomplete outcomes; selective outcome reporting and other sources of bias. Reviewers will attribute answer alternatives “definitely yes”, “probably yes”, “probably not” and “definitely not” for each of the domains. Ultimately, “definitely yes” and “probably yes” will be attributed low risk of bias, whereas “definitely not” and “probably not” mean high risk of bias. Reviewers will solve divergences through discussion, and a third person will judge unsolved divergences.

Definitions of IMMPACT outcome domain

The four IMMPACT domains recommended in 2003 and 2008 which will be captured in this study are listed below, together with their definitions

1. Pain: Includes various aspects of pain evaluation (e.g., intensity of pain, duration and frequency). The global evaluation of pain is a general assessment which examines how the pain changed during the treatment.

2. Physical function: refers to the participant's capacity to conduct their daily activities (e.g., tasks, walks, trips and self-care), strength and resistance.

3. Emotional state: refers to the treatment associated to emotional anguish (e.g., depression, anxiety, anger or irritability).

4. Patient's classification of improvement and satisfaction with the treatment: refers to the participant's feeling with the treatment (that is, if they feel the positive features of the treatment surpass the negative ones). This domain overcomes pain classification only.

Statistical Analysis

The descriptive part includes year of publication, place of study, factor of impact of the journal and items of evaluation of methodological quality. Afterwards, the frequency of measurement of pain, physical function, emotional state and patient satisfaction improvement will be described according to the IMMPACT recommendations.

Thereafter, for each domain, the measurement method is quantized, that is, whether the pain was measured by VAS and / or Van, whether physical function was measured by multidimensional inventory to pain and / or inventory summary of the pain, whether the emotional state was measured by the Beck depression inventory and / or mood state profile, and whether the improvement in patient satisfaction was measured by the patient's overall impression of change. The correct applicability of the instrument will also be quantified (if the domain report was executed by the patient, clinical or third parties). Finally, compliance with IMMPACT will be measured by the attendance of the four domains. It is also planned to quantify the number of IMMPACT domains that will be served, in order to generate a score between 0-4 points. The score will be described on average, standard deviation, median and interquartile range.

The factors associated with compliance with the areas of IMMPACT will be investigated. For this, a logistic regression will be performed considering the domains of IMMPACT as dependent variables and the characteristics of the study as independent variables (year of publication, place of study, periodic impact factor and items of

methodological quality evaluation). The results will be expressed in Odds Ratio with respective 95% confidence intervals.

Factors associated with the IMMPACT score will also be investigated. Depending on the data distribution, analysis of variance (ANOVA) or Kruskal Wallis will be performed. A significant statistical difference will be attributed to cases of $p \leq 0.05$.

Sensitivity analysis will be performed by means of a bootstrap technique. [16] All calculations will run in STATA 14.2.

DISCUSSION

Our survey will evaluate methodologically the outcomes of CRTC which used acupuncture for NOCP. It will provide efficacy estimations for treatments, and assess the quality of evidence in a thorough and consistent way by using recommendations provided by IMMPACT. Our survey's outcomes will be significant for public health and for health professionals all over the world, mainly in Brazil.

Since the publication of IMMPACT, it is not known whether studies using acupuncture as an intervention for chronic pain follow IMMPACT's recommendations. Without consistent and more thorough standard outcome reports for patients in CRTC and NOCP, the authors of such studies will be unable to judge objectively the effects of acupuncture. The data compiled on the use of acupuncture will inform both patients and health professionals about its efficacy and safety. Therefore, multiprofessional care and decision-making based on evidence will be made easier.

This Project aims at exploring some hypotheses to determine the use of IMMPACT recommendations on CRTC–NOCP. After the publication of IMMPACT orientations in August 2003 and later, in 2008, CRTC–NOCP which started recruiting participants as from September 2004 had better reports of main outcomes, regarding IMMPACT domains versus journals with lower impact factors. The main domains were reported by the patient, by the clinician, by a third person or by a combination of these subjects.

ETHICS AND DIFUSION

Ethics is not necessary, as this is protocol for a methodological survey. The survey will be published in a journal and presented in congresses with reviews by peers. The evidence of this study will allow health professionals to verify the efficacy and safety of acupuncture for the treatment of NOCP. Updates of this study should be conducted to inform and orient the practice of health care.

Contributors: LCL is the main researcher who leaded the writing of the manuscript. CCB and LGM are the project manager, co-researcher, who contributed to and writing and review of the manuscript. MTS is co-researcher, and contributed to the writing and review of the manuscript. All the authors have read and approved of the final manuscript.

Acknowledgments: The authors thank Dr. Caio Guimarães for his expert advice.

Sponsorship: This Project has not received any specific funding of any public, private or non-profit agency.

Interest conflict: None.

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Appendix A

Table 1. Search Strategy for database

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 exp Acupuncture Analgesia/
2 exp Acupuncture/
3 acupuncture.mp.
4 1 OR 2 OR 3
5 chronic pain.mp.
6 exp Chronic Pain/
7 exp Chronic Disease/
8 5 OR 6 OR 7
9 4 AND 8

Database: Embase <1974 to 2016 June 28>
Search Strategy:
1 exp acupuncture analgesia/
2 acupuncture.mp.
3 exp acupuncture/
4 1 OR 2 OR 3
5 exp chronic pain/
6 chronic pain.mp.
7 5 OR 6
8 4 AND 7

Database: AMED (Allied and Complementary Medicine) <1985 to June 2016>
Search Strategy:
1 acupuncture.mp.
2 exp Acupuncture/
3 1 OR 2
4 exp Chronic disease/
5 chronic pain.mp.
6 4 OR 5
7 3 AND 6

Database: CINAHL
Search Strategy:
1 (MH "Acupuncture+")
2 (MH "Acupuncture Analgesia")
3 1 OR 2
4 (MH "Chronic Pain")
5 3 AND 4

Database: Cochrane Library
Search Strategy:
1 "acupuncture":ti,ab,kw
2 "acupuncture analgesia":ti,ab,kw

3 1 OR 2
4 "chronic pain":ti,ab,kw
5 3 AND 4

Database: Web of Science <1976 to July 2016>
Search Strategy:
1 acupuncture
2 *acupuncture*
3 1 OR 2
4 chronic pain
5 chronic *pain*
6 4 OR 5
7 3 AND 6

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract			not applicable
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		☐	not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		10
Sponsor	5b	Provide name for the review funder and/or sponsor		☐	not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		☐	not applicable
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐		5

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		5, 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		5, 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐		5, 6
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐		7
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		8, 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐		8, 9
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐		9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		9

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		7, 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		☐	not applicable

BMJ Open

USE OF IMMPACT DOMAINS IN CLINICAL TRIALS OF ACUPUNCTURE FOR CHRONIC PAIN: A PROTOCOL FOR A METHODOLOGICAL SURVEY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014904.R2
Article Type:	Protocol
Date Submitted by the Author:	25-Jun-2017
Complete List of Authors:	Mazzei, Lauren; Universidade de Sorocaba, Programa de Pós-Graduação em Ciências Farmacêuticas Bergamaschi, Cristiane; University of Sorocaba, Pharmaceutical Science Silva, Marcus; Federal University of Amazonas, Clinical Epidemiology Lopes, Luciane; UNISO, Pharmacie Science
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Complementary medicine, Evidence based practice
Keywords:	Acupuncture, Chronic Pain, Methodological Survey

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2588 words

SUMMARY

INTRODUCTION: Pain is one of the most common and most debilitating complaints among patients. They affect the individual, their relationship with friends and family, their work force, and their sociability. Acupuncture is one of the therapeutic resources for managing chronic pain. Given the variability of outcome measures in Controlled Randomized Clinical Trials on Non-Oncologic Chronic Pain (CRCT-NOCP), the Initiative in Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) recommends six domains to be covered in evaluating the effectiveness of treatments for chronic pain.

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Keywords: Acupuncture. Chronic Pain. Methodological Survey.

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- ✓ Acupuncture can be an effective therapy in chronic pain control, avoiding costly expenses with analgesic medication which generate dependence (opioids), or limiting adverse effects as in the case of non-steroid anti-inflammatories (gastric ulcer and cardiovascular events) that have a direct impact in the patient's life. Therefore, checking compliance with IMMPACT recommendations in CRCT about NOCP may appraise the quality of the evidence and provide greater transparency in decisions regarding the use of acupuncture as a viable alternative in this clinical condition. It can also guide physicians in clinical practice decision making.
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Even showing quality, CRCT with adequate randomization and blinding may not provide the best approach for the development of strong evidence base for managing pain, in case the outcomes and its tools are not adequate. [11] Such limitations have been recognized internationally, leading to the development of the Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) in 2002.

The initiative gathered 27 experts from universities, governmental agencies and pharmaceutical industry, who identified consensually a nucleus of six outcome domains that should be considered in CRCT for chronic pain. [12] The outcome domains considered were: (1) pain; (2) physical function; (3) emotional state; (4) evaluation of the participants regarding improvement and satisfaction with treatment; (5) adverse symptoms; and (6) the participant's willingness, but the first four domains listed as main. [13]

The establishment of a standard set of outcome domains in CRCT about chronic pain encourages researchers to consider chronic pain as a complex phenomenon which affects patients in multiple dimensions. It protects against the polarization of selective outcomes, a common problem in all medical literature. It makes systematic reviews and Meta analyses easier, which allows researchers to generate more precise estimations of treatment effects due to sharing common outcomes of individual trials. [14]

Variability in outcome measures in CRCT about NOCP generates inaccuracies in the effectiveness of certain treatments. Although the recommendation of IMMPACT was published in 2003 and updated in 2008, there is no information on whether subsequent clinical trials published comply with IMMPACT recommendations on their outcome measures.

The general aim of this project is to verify whether methodological quality of outcome reporting in published trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes which were executed as of September 2004 when acupuncture was used as a treatment.

METHODS

Study Design

The study comprises a methodological survey of randomized clinical trials which used acupuncture for the treatment of chronic pain. The methodological survey is a type of study on method enquiry, with data collection form selected CRCT, not based on questionnaires but using systematic methods in its execution.

Research question

The question that guides this study was formulated using the PICO strategy, which represents an acronym for Patient, Intervention, Comparison and Outcomes. In evidence-based practice, these four components are the fundamental elements of the research question and the construction of the question for the bibliographic search for evidence. Adequate research question allows the correct definition of what information (evidence) is necessary to solve the clinical research question, maximizes the retrieval of evidence in the databases, focuses the scope of the research and avoids unnecessary searches. [15]

Using the PICO strategy, the question of this survey was: RCT with individuals with Non-Oncologic Chronic Pain (*population*) treated with acupuncture (*intervention*), and where the comparator used was acupuncture sham or not acupuncture (*comparison*), they reported the domains of IMMPACT recommendations (*outcome*)?

Reference Sources and Search

All trials already included in CRCT-NOCP, published as of September 2004, selected in the systematic review carried out by Vickers et al. [16] Additional research

will be performed in studies dating as from January 2011 and 6 months before the systematic review of the comprehensive search date on the theme (considering delay in indexing) to nowadays. The search for eligible studies will be accomplished by systematic research of database, namely Lilacs, CINAHL, EMBASE, MEDLINE, AMED, Web of Science, Clinical Trials and Cochrane Central Registry of Controlled Trials, with a defined search strategy, free of idiom restriction.

We shall combine the main terms "Chronic Pain" and "Acupuncture" indexed in the MeSH system. Firstly, we will search the isolate terms and their synonyms, and then we will make a second search, combining and crossing the terms. Appendix A, Table 1.

We will verify the reference or citation list found in secondary studies to identify possibly eligible studies. When necessary, we shall contact the authors of the main studies to obtain further information.

Study Eligibility Criteria

The eligibility criteria for this study will be the same as those adopted in the systematic review published in 2012.

Design: controlled randomized clinical trials, whose patient recruitment occurred from September 2004 and whose number of patients is equal or more than 100.

Clinical condition: studies which include patients aged 18 or older, with non-oncologic chronic pain. Eligible pain conditions: Osteoarthritis, chronic or recurrent headaches, specific and nonspecific shoulder pains, and nonspecific back or neck pain. For osteoarthritis or headaches, it will not be necessary the duration of the pain, since both are of a chronic nature. For pain in the shoulder, back and neck, the pain episode should be at least four weeks in duration.

Intervention: the studies should include a group of patients treated with acupuncture, where acupuncture points or trigger points were stimulated with acupuncture needles, and another group where patients were treated with sham acupuncture or no acupuncture, and studies where the choice blinding is unmistakable and adequate.

Exclusion Criteria: The following trials are to be excluded: neck or back pains associated with specific clinical conditions (e.g., fractures resulting from ostheoporosis).

Determination of Eligibility

Two reviewers, in pairs, will evaluate independently whether summaries and titles are according to the eligibility criteria. Differences are to be solved by consensus among all reviewers. To assess the agreement of the selection we will use Kappa Test, given that kappa values between 0,40 and 0,59 are to be considered weak agreement, between 0,60 and 0,74 medium agreement, and 0,75 or more excellent agreement.

In order to exclude doubled articles, one reviewer will analyze all the eligible articles and identify those which have one or more authors in common. In case of doubled publication, we will use the article with most complete data.

Data Extraction

We will adopt an Excel spreadsheet for the abstraction of data, to be used by two reviewers separately. A third reviewer will check the Excel spreadsheet to ensure the coherence of the answers obtained among collaborators and use the consensus when necessary.

For articles published only in summary or for those with important information missing, we will look for complete information about methods and results by contacting the authors.

Two reviewers will be calibrated by the extraction of at least three articles and next, will perform the consensus, in pairs and independently. This procedure shall occur until reviewers are able to extract the data. The collected data will be: name of the first author, date of publication, country of origin, impact of the journal, recruitment date of the first participant, presence of outcome domains IMMPACT, and the tools used for measuring the outcome domains, method of acupuncture, clinical condition of the patient, duration of treatment. Besides this, the study will check if fundamental outcomes are reported by the patient (ORP), if clinical outcomes are reported (COR), if the outcome was reported by a third person (ORT), or a combination of the items above.

The data will be recorded to be transferred to a statistical analysis program later. A regression analysis will be conducted to explore factors that may be associated with the presence of outcome domains according to IMMPACT recommendations.

Risk of Bias

A modified version of Cochrane for risk of bias will be used. [14 17] Reviewers will evaluate the risk of bias for each randomized trial independently, according to the following criteria: generation of random sequence, hiding of the choices, blinding of participants and professionals, blinding of outcome evaluators, if outcomes were reported adequately; incomplete outcomes; selective outcome reporting and other sources of bias. Reviewers will attribute answer alternatives "definitely yes", "probably yes", "probably not" and "definitely not" for each of the domains. [18] Ultimately, "definitely yes" and "probably yes" will be attributed low risk of bias, whereas "definitely not" and "probably not" mean high risk of bias. Reviewers will solve divergences through discussion, and a third person will judge unsolved divergences.

Definitions of IMMPACT outcome domain

The four IMMPACT domains recommended in 2003 and 2008 which will be captured in this study are listed below, together with their definitions

1. Pain: Includes various aspects of pain evaluation (e.g., intensity of pain, duration and frequency). The global evaluation of pain is a general assessment which examines how the pain changed during the treatment.

2. Physical function: refers to the participant's capacity to conduct their daily activities (e.g., tasks, walks, trips and self-care), strength and resistance.

3. Emotional state: refers to the treatment associated to emotional anguish (e.g., depression, anxiety, anger or irritability).

4. Patient's classification of improvement and satisfaction with the treatment: refers to the participant's feeling with the treatment (that is, if they feel the positive features of the treatment surpass the negative ones). This domain overcomes pain classification only.

Statistical Analysis

The statistical analyzes carried out in this survey will aim to identify the factors associated with the change in reporting or adherence to the IMMPACT recommendations, in RCT made since its publication.

The descriptive part includes year of publication, place of study, factor of impact of the journal and items of evaluation of methodological quality. These factors will be highlighted as they may influence the adherence of the IMMPACT recommendations. Afterwards, the frequency of measurement of pain, physical function, emotional state and patient satisfaction improvement will be described according to the IMMPACT recommendations.

Thereafter, for each domain, the measurement method is quantized, that is, whether the pain was measured by VAS and / or VAN, whether physical function was measured by multidimensional inventory to pain and / or inventory summary of the pain, whether the emotional state was measured by the Beck depression inventory and / or mood state profile, and whether the improvement in patient satisfaction was measured by the patient's overall impression of change. The correct applicability of the instrument will also be quantified (if the domain report was executed by the patient, clinical or third parties). Finally, compliance with IMMPACT will be measured by the attendance of the four domains. It is also planned to quantify the number of IMMPACT domains that will be served, in order to generate a score between 0-4 points. The score will be described on average, standard deviation, median and interquartile range.

A score of 0 will be given when the study does not report any of the domains recommended by IMMPACT, score 1, when reporting only one of the recommended domains; Score 2 when reporting two of the recommended domains; Score 3, when reporting three of the recommended domains; and score 4 when reporting the four major domains recommended by IMMPACT.

The factors associated with compliance with the areas of IMMPACT will be investigated. For this, a logistic regression will be performed considering the domains of IMMPACT as dependent variables and the characteristics of the study as independent variables (year of publication, place of study, periodic impact factor and items of methodological quality evaluation). For a good regression analysis, a minimum of 10 references is necessary, which will not be a problem since we will include previous SR

studies. The results will be expressed in Odds Ratio with respective 95% confidence intervals.

Factors associated with the IMMPACT score will also be investigated. Depending on the data distribution, analysis of variance (ANOVA) or Kruskal Wallis will be performed. A significant statistical difference will be attributed to cases of $p \leq 0.05$.

Sensitivity analysis will be performed for all calculations, by means of a bootstrap technique, which will verify the consistency and robustness of the findings. [19] All calculations will run in STATA 14.2.

DISCUSSION

Our survey will evaluate methodologically the outcomes of RCT which used acupuncture for NOCP. We will check whether methodological quality of outcome reporting in published trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes when acupuncture was used as a treatment.. Our survey's outcomes will be significant for public health and for health professionals all over the world, mainly in Brazil.

Since the publication of IMMPACT, it is not known whether studies using acupuncture as an intervention for chronic pain follow IMMPACT's recommendations. Without consistent and more thorough standard outcome reports for patients in CRTC and NOCP, the authors of such studies will be unable to judge objectively the effects of acupuncture. The data compiled on the use of acupuncture will inform both patients and health professionals about its efficacy and safety. Therefore, multiprofessional care and decision-making based on evidence will be made easier.

This Project aims at exploring some hypotheses to determine the use of IMMPACT recommendations on CRTC–NOCP. After the publication of IMMPACT orientations in August 2003 and later, in 2008, CRTC–NOCP which started recruiting participants as from September 2004 had better reports of main outcomes, regarding IMMPACT domains versus journals with lower impact factors. The main domains were reported by the patient, by the clinician, by a third person or by a combination of these subjects.

ETHICS AND DIFUSION

Ethics is not necessary, as this is protocol for a methodological survey. The survey will be published in a journal and presented in congresses with reviews by peers. The evidence of this study will allow health professionals to verify the efficacy and safety of acupuncture for the treatment of NOCP. Updates of this study should be conducted to inform and orient the practice of health care.

Contributors: LCL is the main researcher who leaded the writing of the manuscript. CCB and LGM are the project manager, co-researcher, who contributed to and writing and review of the manuscript. MTS is co-researcher, and contributed to the writing and review of the manuscript. All the authors have read and approved of the final manuscript.

Acknowledgments: The authors thank Dr. Caio Guimarães for his expert advice.

Sponsorship: This Project has not received any specific funding of any public, private or non-profit agency.

Interest conflict: None.

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Appendix A

Table 1. Search Strategy for database

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 exp Acupuncture Analgesia/
2 exp Acupuncture/
3 acupuncture.mp.
4 1 OR 2 OR 3
5 chronic pain.mp.
6 exp Chronic Pain/
7 exp Chronic Disease/
8 5 OR 6 OR 7
9 4 AND 8

Database: Embase <1974 to 2016 June 28>
Search Strategy:
1 exp acupuncture analgesia/
2 acupuncture.mp.
3 exp acupuncture/
4 1 OR 2 OR 3
5 exp chronic pain/
6 chronic pain.mp.
7 5 OR 6
8 4 AND 7

Database: AMED (Allied and Complementary Medicine) <1985 to June 2016>
Search Strategy:
1 acupuncture.mp.
2 exp Acupuncture/
3 1 OR 2
4 exp Chronic disease/
5 chronic pain.mp.
6 4 OR 5
7 3 AND 6

Database: CINAHL
Search Strategy:
1 (MH "Acupuncture+")
2 (MH "Acupuncture Analgesia")
3 1 OR 2
4 (MH "Chronic Pain")
5 3 AND 4

Database: Cochrane Library
Search Strategy:
1 "acupuncture":ti,ab,kw
2 "acupuncture analgesia":ti,ab,kw

3 1 OR 2
4 "chronic pain":ti,ab,kw
5 3 AND 4

Database: Web of Science <1976 to July 2016>
Search Strategy:
1 acupuncture
2 *acupuncture*
3 1 OR 2
4 chronic pain
5 chronic *pain*
6 4 OR 5
7 3 AND 6

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract			not applicable
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		☐	not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		10
Sponsor	5b	Provide name for the review funder and/or sponsor		☐	not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		☐	not applicable
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐		5

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		5, 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		5, 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐		5, 6
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐		7
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		8, 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐		8, 9
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐		9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		9

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		7, 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		☐	not applicable

BMJ Open

USE OF IMMPACT DOMAINS IN CLINICAL TRIALS OF ACUPUNCTURE FOR CHRONIC PAIN: A PROTOCOL FOR A METHODOLOGICAL SURVEY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014904.R3
Article Type:	Protocol
Date Submitted by the Author:	02-Aug-2017
Complete List of Authors:	Mazzei, Lauren; Universidade de Sorocaba, Programa de Pós-Graduação em Ciências Farmacêuticas Bergamaschi, Cristiane; University of Sorocaba, Pharmaceutical Science Silva, Marcus; Federal University of Amazonas, Clinical Epidemiology Lopes, Luciane; UNISO, Pharmacie Science
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Complementary medicine, Evidence based practice
Keywords:	Acupuncture, Chronic Pain, Methodological Survey

USE OF IMMPACT DOMAINS IN CLINICAL TRIALS OF ACUPUNCTURE FOR CHRONIC PAIN: A PROTOCOL FOR A METHODOLOGICAL SURVEY

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2588 words

SUMMARY

INTRODUCTION: Pain is one of the most common and most debilitating complaints among patients. They affect the individual, their relationship with friends and family, their work force, and their sociability. Acupuncture is one of the therapeutic resources for managing chronic pain. Given the variability of outcome measures in Controlled Randomized Clinical Trials on Non-Oncologic Chronic Pain (CRCT-NOCP), the Initiative in Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) recommends six domains to be covered in evaluating the effectiveness of treatments for chronic pain.

OBJECTIVE: The main objective of this study is to check whether methodological quality of outcome reporting in published trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes when acupuncture was used as a treatment.

METHOD: This is a methodological study. We will systematically search for eligible studies in specific database with a defined strategy. We are to use terms of MeSH "acupuncture", "chronic pain" and its similar terms, without idiom restrictions. Eligible studies include those which randomized and chose NOCP patients to be treated with acupuncture or control (sham acupuncture or no acupuncture), recruited after September 2004, number of patients equal or more than 100. The measured outcomes are to be the presence of outcome domains recommended by IMMPACT, domains reported by patient or clinician, tools used to measure such domains, besides other features of the studies. We shall conduct a regression analysis to explore factors which can be associated with the presence of outcome domains according to IMMPACT recommendations.

ETHICS AND DISSEMINATION: This survey will be submitted to presentation in congresses and publishing in a scientific journal. The evidence obtained in this study will allow us to measure the quality of the evidence and greater transparency in decisions regarding the use of acupuncture as a viable alternative to managing chronic pain.

Keywords: Acupuncture. Chronic Pain. Methodological Survey.

Strong Points and Limitations of this Study

- ✓ This is the first study to evaluate the outcome domains used in CRCT using acupuncture as intervention to the treatment of NOCP.

- ✓ Acupuncture can be an effective therapy in chronic pain control, avoiding costly expenses with analgesic medication which generate dependence (opioids), or limiting adverse effects as in the case of non-steroid anti-inflammatories (gastric ulcer and cardiovascular events) that have a direct impact in the patient's life. Therefore, checking compliance with IMMPACT recommendations in CRCT about NOCP may appraise the quality of the evidence and provide greater transparency in decisions regarding the use of acupuncture as a viable alternative in this clinical condition. It can also guide physicians in clinical practice decision making.
- ✓ The methods contain explicit eligibility criteria, a comprehensive research and a double independent selection, including independent appraisal of bias risk.
- ✓ Primary studies are probably limited in conception and outcome measures and thus, they have high bias risk. Besides, techniques or point categories used in acupuncture may be uncertain or varied in different studies.
- ✓ This enquiry has not received any specific sponsorship from any public, private or non-profit agency.

INTRODUCTION

Non-Oncologic Chronic Pain (NOCP) is defined as a persisting painful feeling for more than some months, which may be associated to traumas and illnesses or not. [1] It is estimated that 18, 9% of the world population present chronic pain. It is one of the most common complaints among patients, affecting not only the subject in their individuality, but also in a general way. [2]

It is regarded as a health problem that consumes 22% of primary health appointments on average. In the United States, costs with pain medication are around US$17, 8 billion a year. [3] In Canada the average cost is of $ 1,462 per individual monthly with chronic pain on waiting lists [4] and of € 1,883.30 per indivudual, adult in Portugal. [5]

Acupuncture is one of the resources that compose the National Policy of Integrated and Supplementary Practices (NPISP) IN Brazil. It is a possible therapy in managing chronic pain with sensitive cost reduction to the government and adverse effect reduction to the patient. [6] The World Health Organization (WHO) has launched

a strategy for the period 2014-2023 to integrate to traditional medicine and supplement the health system in a safe, respectful, accessible and effective way. [7]

The search for international guidelines approaching the use of acupuncture for NOCP in the adult population results in few findings or in conflicting recommendations. Acupuncture is recommended as an adjunct to conventional treatment of NOCP, but only the American guidelines specify the moment in which it should be used within the conventional drug treatment flow. [8] [9] [10] [2]

Among the policies we looked up, the recommendation of acupuncture for many painful conditions is based on low quality evidence due to the diversity in the methodology of CRCT. [2 8-10] Besides this, such guidelines do not discriminate the power of the recommendation, except for those in Scotland and Canada. [2 8]

Even showing quality, CRCT with adequate randomization and blinding may not provide the best approach for the development of strong evidence base for managing pain, in case the outcomes and its tools are not adequate. [11] Such limitations have been recognized internationally, leading to the development of the Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) in 2002.

The initiative gathered 27 experts from universities, governmental agencies and pharmaceutical industry, who identified consensually a nucleus of six outcome domains that should be considered in CRCT for chronic pain. [12] The outcome domains considered were: (1) pain; (2) physical function; (3) emotional state; (4) evaluation of the participants regarding improvement and satisfaction with treatment; (5) adverse symptoms; and (6) the participant's willingness, but the first four domains listed as main. [13]

The establishment of a standard set of outcome domains in CRCT about chronic pain encourages researchers to consider chronic pain as a complex phenomenon which affects patients in multiple dimensions. It protects against the polarization of selective outcomes, a common problem in all medical literature. It makes systematic reviews and Meta analyses easier, which allows researchers to generate more precise estimations of treatment effects due to sharing common outcomes of individual trials. [14]

Variability in outcome measures in CRCT about NOCP generates inaccuracies in the effectiveness of certain treatments. Although the recommendation of IMMPACT was published in 2003 and updated in 2008, there is no information on whether subsequent clinical trials published comply with IMMPACT recommendations on their outcome measures.

The general aim of this project is to verify whether methodological quality of outcome reporting in published trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes which were executed as of September 2004 when acupuncture was used as a treatment.

METHODS

Study Design

The study comprises a methodological survey of randomized clinical trials which used acupuncture for the treatment of chronic pain. The methodological survey is a type of study on method enquiry, with data collection form selected CRCT, not based on questionnaires but using systematic methods in its execution.

Research question

The question that guides this study was formulated using the PICO strategy, which represents an acronym for Patient, Intervention, Comparison and Outcomes. In evidence-based practice, these four components are the fundamental elements of the research question and the construction of the question for the bibliographic search for evidence. Adequate research question allows the correct definition of what information (evidence) is necessary to solve the clinical research question, maximizes the retrieval of evidence in the databases, focuses the scope of the research and avoids unnecessary searches. [15]

Using the PICO strategy, the question of this survey was: RCT with individuals with Non-Oncologic Chronic Pain (*population*) treated with acupuncture (*intervention*), and where the comparator used was acupuncture sham or not acupuncture (*comparison*), they reported the domains of IMMPACT recommendations (*outcome*).

Reference Sources and Search

All trials already included in CRCT-NOCP, published as of September 2004, selected in the systematic review carried out by Vickers et al. [16] Additional research

will be performed in studies dating as from January 2011 and 6 months before the systematic review of the comprehensive search date on the theme (considering delay in indexing) to nowadays. The search for eligible studies will be accomplished by systematic research of database, namely Lilacs, CINAHL, EMBASE, MEDLINE, AMED, Web of Science, Clinical Trials and Cochrane Central Registry of Controlled Trials, with a defined search strategy, free of idiom restriction.

We shall combine the main terms "Chronic Pain" and "Acupuncture" indexed in the MeSH system. Firstly, we will search the isolate terms and their synonyms, and then we will make a second search, combining and crossing the terms. Appendix A, Table 1.

We will verify the reference or citation list found in secondary studies to identify possibly eligible studies. When necessary, we shall contact the authors of the main studies to obtain further information.

Study Eligibility Criteria

The eligibility criteria for this study will be the same as those adopted in the systematic review published in 2012.

Design: controlled randomized clinical trials, whose patient recruitment occurred from September 2004 and whose number of patients is equal or more than 100.

Clinical condition: studies which include patients aged 18 or older, with non-oncologic chronic pain. Eligible pain conditions: Osteoarthritis, chronic or recurrent headaches, specific and nonspecific shoulder pains, and nonspecific back or neck pain. For osteoarthritis or headaches, it will not be necessary the duration of the pain, since both are of a chronic nature. For pain in the shoulder, back and neck, the pain episode should be at least four weeks in duration.

Intervention: the studies should include a group of patients treated with acupuncture, where acupuncture points or trigger points were stimulated with acupuncture needles, and another group where patients were treated with sham acupuncture or no acupuncture, and studies where the choice blinding is unmistakable and adequate.

Exclusion Criteria: The following trials are to be excluded: neck or back pains associated with specific clinical conditions (e.g., fractures resulting from ostheoporosis).

Determination of Eligibility

Two reviewers, in pairs, will evaluate independently whether summaries and titles are according to the eligibility criteria. Differences are to be solved by consensus among all reviewers. To assess the agreement of the selection we will use Kappa Test, given that kappa values between 0,40 and 0,59 are to be considered weak agreement, between 0,60 and 0,74 medium agreement, and 0,75 or more excellent agreement.

In order to exclude doubled articles, one reviewer will analyze all the eligible articles and identify those which have one or more authors in common. In case of doubled publication, we will use the article with most complete data.

Data Extraction

We will adopt an Excel spreadsheet for the abstraction of data, to be used by two reviewers separately. A third reviewer will check the Excel spreadsheet to ensure the coherence of the answers obtained among collaborators and use the consensus when necessary.

For articles published only in summary or for those with important information missing, we will look for complete information about methods and results by contacting the authors.

Two reviewers will be calibrated by the extraction of at least three articles and next, will perform the consensus, in pairs and independently. This procedure shall occur until reviewers are able to extract the data. The collected data will be: name of the first author, date of publication, country of origin, impact of the journal, recruitment date of the first participant, presence of outcome domains IMMPACT, and the tools used for measuring the outcome domains, method of acupuncture, clinical condition of the patient, duration of treatment. Besides this, the study will check if fundamental outcomes are reported by the patient (ORP), if clinical outcomes are reported (COR), if the outcome was reported by a third person (ORT), or a combination of the items above.

The data will be recorded to be transferred to a statistical analysis program later. A regression analysis will be conducted to explore factors that may be associated with the presence of outcome domains according to IMMPACT recommendations.

Risk of Bias

A modified version of Cochrane for risk of bias will be used. [14 17] Reviewers will evaluate the risk of bias for each randomized trial independently, according to the following criteria: generation of random sequence, hiding of the choices, blinding of participants and professionals, blinding of outcome evaluators, if outcomes were reported adequately; incomplete outcomes; selective outcome reporting and other sources of bias. Reviewers will attribute answer alternatives "definitely yes", "probably yes", "probably not" and "definitely not" for each of the domains. [18] Ultimately, "definitely yes" and "probably yes" will be attributed low risk of bias, whereas "definitely not" and "probably not" mean high risk of bias. Reviewers will solve divergences through discussion, and a third person will judge unsolved divergences.

Definitions of IMMPACT outcome domain

The four IMMPACT domains recommended in 2003 and 2008 which will be captured in this study are listed below, together with their definitions

1. Pain: Includes various aspects of pain evaluation (e.g., intensity of pain, duration and frequency). The global evaluation of pain is a general assessment which examines how the pain changed during the treatment.

2. Physical function: refers to the participant's capacity to conduct their daily activities (e.g., tasks, walks, trips and self-care), strength and resistance.

3. Emotional state: refers to the treatment associated to emotional anguish (e.g., depression, anxiety, anger or irritability).

4. Patient's classification of improvement and satisfaction with the treatment: refers to the participant's feeling with the treatment (that is, if they feel the positive features of the treatment surpass the negative ones). This domain overcomes pain classification only.

Thereafter, for each domain, the measurement method is quantized, that is, whether the pain was measured by VAS and / or VAN, whether physical function was measured by multidimensional inventory to pain and / or inventory summary of the pain, whether the emotional state was measured by the Beck depression inventory and /

or mood state profile, and whether the improvement in patient satisfaction was measured by the patient's overall impression of change. The correct applicability of the instrument will also be quantified (if the domain report was executed by the patient, clinical or third parties).

Statistical Analysis

The statistical analyzes carried out in this survey will aim to identify the factors associated with the change in reporting or adherence to the IMMPACT recommendations, in RCT made since its publication.

The descriptive part includes year of publication, place of study, factor of impact of the journal and items of evaluation of methodological quality. These factors will be highlighted as they may influence the adherence of the IMMPACT recommendations. Afterwards, the frequency of measurement of pain, physical function, emotional state and patient satisfaction improvement will be described according to the IMMPACT recommendations.

Compliance with IMMPACT will be measured by the attendance of the four main domains. It is also planned to quantify the number of IMMPACT domains that will be served, in order to generate a score between 0-4 points. The score will be described on average, standard deviation, median and interquartile range.

A score of 0 will be given when the study does not report any of the domains recommended by IMMPACT, score 1, when reporting only one of the recommended domains; Score 2 when reporting two of the recommended domains; Score 3, when reporting three of the recommended domains; and score 4 when reporting the four major domains recommended by IMMPACT.

The factors associated with compliance with the areas of IMMPACT will be investigated. For this, a logistic regression will be performed considering the domains of IMMPACT as dependent variables and the characteristics of the study as independent variables (year of publication, place of study, periodic impact factor and items of methodological quality evaluation). For a good regression analysis, a minimum of 10 references is necessary, which will not be a problem since we will include previous SR studies. The results will be expressed in Odds Ratio with respective 95% confidence intervals.

Factors associated with the IMMPACT score will also be investigated. Depending on the data distribution, one-tailed analysis of variance (ANOVA) or one-tailed Kruskal Wallis will be performed. A significant statistical difference will be attributed to cases of $p \leq 0.05$.

All calculations will run in STATA 14.2.

DISCUSSION

Our survey will evaluate methodologically the outcomes of RCT which used acupuncture for NOCP. We will check whether methodological quality of outcome reporting in published trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes when acupuncture was used as a treatment. Our survey's outcomes will be significant for public health and for health professionals all over the world, mainly in Brazil.

Since the publication of IMMPACT, it is not known whether studies using acupuncture as an intervention for chronic pain follow IMMPACT's recommendations. Without consistent and more thorough standard outcome reports for patients in CRTC and NOCP, the authors of such studies will be unable to judge objectively the effects of acupuncture. The data compiled on the use of acupuncture will inform both patients and health professionals about its efficacy and safety. Therefore, multiprofessional care and decision-making based on evidence will be made easier.

This Project aims at exploring some hypotheses to determine the use of IMMPACT recommendations on CRTC–NOCP. After the publication of IMMPACT orientations in August 2003 and later, in 2008, CRTC–NOCP which started recruiting participants as from September 2004 had better reports of main outcomes, regarding IMMPACT domains versus journals with lower impact factors. The main domains were reported by the patient, by the clinician, by a third person or by a combination of these subjects.

ETHICS AND DIFUSION

Ethics is not necessary, as this is protocol for a methodological survey. The survey will be published in a journal and presented in congresses with reviews by peers. The evidence of this study will allow health professionals to verify the efficacy and

safety of acupuncture for the treatment of NOCP. Updates of this study should be conducted to inform and orient the practice of health care.

Contributors: LCL is the main researcher who leaded the writing of the manuscript. CCB and LGM are the project manager, co-researcher, who contributed to and writing and review of the manuscript. MTS is co-researcher, and contributed to the writing and review of the manuscript. All the authors have read and approved of the final manuscript.

Acknowledgments: The authors thank Dr. Caio Guimarães for his expert advice.

Sponsorship: This Project has not received any specific funding of any public, private or non-profit agency.

Interest conflict: None.

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Appendix A

Table 1. Search Strategy for database

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 exp Acupuncture Analgesia/
2 exp Acupuncture/
3 acupuncture.mp.
4 1 OR 2 OR 3
5 chronic pain.mp.
6 exp Chronic Pain/
7 exp Chronic Disease/
8 5 OR 6 OR 7
9 4 AND 8

Database: Embase <1974 to 2016 June 28>
Search Strategy:
1 exp acupuncture analgesia/
2 acupuncture.mp.
3 exp acupuncture/
4 1 OR 2 OR 3
5 exp chronic pain/
6 chronic pain.mp.
7 5 OR 6
8 4 AND 7

Database: AMED (Allied and Complementary Medicine) <1985 to June 2016>
Search Strategy:
1 acupuncture.mp.
2 exp Acupuncture/
3 1 OR 2
4 exp Chronic disease/
5 chronic pain.mp.
6 4 OR 5
7 3 AND 6

Database: CINAHL
Search Strategy:
1 (MH "Acupuncture+")
2 (MH "Acupuncture Analgesia")
3 1 OR 2
4 (MH "Chronic Pain")
5 3 AND 4

Database: Cochrane Library
Search Strategy:
1 "acupuncture":ti,ab,kw
2 "acupuncture analgesia":ti,ab,kw

3 1 OR 2
4 "chronic pain":ti,ab,kw
5 3 AND 4

Database: Web of Science <1976 to July 2016>
Search Strategy:
1 acupuncture
2 *acupuncture*
3 1 OR 2
4 chronic pain
5 chronic *pain*
6 4 OR 5
7 3 AND 6

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract			not applicable
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		☐	not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		10
Sponsor	5b	Provide name for the review funder and/or sponsor		☐	not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		☐	not applicable
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐		5

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		5, 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		5, 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐		5, 6
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐		7
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		8, 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐		8, 9
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐		9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		9

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		7, 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		☐	not applicable

BMJ Open

USE OF IMMPACT DOMAINS IN CLINICAL TRIALS OF ACUPUNCTURE FOR CHRONIC PAIN: A PROTOCOL FOR A METHODOLOGICAL SURVEY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014904.R4
Article Type:	Protocol
Date Submitted by the Author:	15-Aug-2017
Complete List of Authors:	Mazzei, Lauren; Universidade de Sorocaba, Programa de Pós-Graduação em Ciências Farmacêuticas Bergamaschi, Cristiane; University of Sorocaba, Pharmaceutical Science Silva, Marcus; Federal University of Amazonas, Clinical Epidemiology Lopes, Luciane; UNISO, Pharmacie Science
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Complementary medicine, Evidence based practice
Keywords:	Acupuncture, Chronic Pain, Methodological Survey

USE OF IMMPACT DOMAINS IN CLINICAL TRIALS OF ACUPUNCTURE FOR CHRONIC PAIN: A PROTOCOL FOR A METHODOLOGICAL SURVEY

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2562 words

SUMMARY

INTRODUCTION: Pain is one of the most common and most debilitating complaints among patients. They affect the individual, their relationship with friends and family, their work force, and their sociability. Acupuncture is one of the therapeutic resources for managing chronic pain. Given the variability of outcome measures in Controlled Randomized Clinical Trials on Non-Oncologic Chronic Pain (CRCT-NOCP), the Initiative in Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) recommends six domains to be covered in evaluating the effectiveness of treatments for chronic pain.

OBJECTIVE: The main objective of this study is to check whether methodological quality of outcome reporting in published trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes when acupuncture was used as a treatment.

METHOD: This is a methodological study. We will systematically search for eligible studies in specific database with a defined strategy. We are to use terms of MeSH "acupuncture", "chronic pain" and its similar terms, without idiom restrictions. Eligible studies include those which randomized and chose NOCP patients to be treated with acupuncture or control (sham acupuncture or no acupuncture), recruited after September 2004, number of patients equal or more than 100. The measured outcomes are to be the presence of outcome domains recommended by IMMPACT, domains reported by patient or clinician, tools used to measure such domains, besides other features of the studies. We shall conduct a regression analysis to explore factors which can be associated with the presence of outcome domains according to IMMPACT recommendations.

ETHICS AND DISSEMINATION: This survey will be submitted to presentation in congresses and publishing in a scientific journal. The evidence obtained in this study will allow us to measure the quality of the evidence and greater transparency in decisions regarding the use of acupuncture as a viable alternative to managing chronic pain.

Keywords: Acupuncture. Chronic Pain. Methodological Survey.

Strong Points and Limitations of this Study

- ✓ This is the first study to evaluate the outcome domains used in CRCT using acupuncture as intervention to the treatment of NOCP.

- ✓ Acupuncture can be an effective therapy in chronic pain control, avoiding costly expenses with analgesic medication which generate dependence (opioids), or limiting adverse effects as in the case of non-steroid anti-inflammatories (gastric ulcer and cardiovascular events) that have a direct impact in the patient's life. Therefore, checking compliance with IMMPACT recommendations in CRCT about NOCP may appraise the quality of the evidence and provide greater transparency in decisions regarding the use of acupuncture as a viable alternative in this clinical condition. It can also guide physicians in clinical practice decision making.
- ✓ The methods contain explicit eligibility criteria, a comprehensive research and a double independent selection, including independent appraisal of bias risk.
- ✓ Primary studies are probably limited in conception and outcome measures and thus, they have high bias risk. Besides, techniques or point categories used in acupuncture may be uncertain or varied in different studies.
- ✓ This enquiry has not received any specific sponsorship from any public, private or non-profit agency.

INTRODUCTION

Non-Oncologic Chronic Pain (NOCP) is defined as a persisting painful feeling for more than some months, which may be associated to traumas and illnesses or not. [1] It is estimated that 18, 9% of the world population present chronic pain. It is one of the most common complaints among patients, affecting not only the subject in their individuality, but also in a general way. [2]

It is regarded as a health problem that consumes 22% of primary health appointments on average. In the United States, costs with pain medication are around US$17, 8 billion a year. [3] In Canada the average cost is of $ 1,462 per individual monthly with chronic pain on waiting lists [4] and of € 1,883.30 per indivudual, adult in Portugal. [5]

Acupuncture is one of the resources that compose the National Policy of Integrated and Supplementary Practices (NPISP) IN Brazil. It is a possible therapy in managing chronic pain with sensitive cost reduction to the government and adverse effect reduction to the patient. [6] The World Health Organization (WHO) has launched

a strategy for the period 2014-2023 to integrate to traditional medicine and supplement the health system in a safe, respectful, accessible and effective way. [7]

The search for international guidelines approaching the use of acupuncture for NOCP in the adult population results in few findings or in conflicting recommendations. Acupuncture is recommended as an adjunct to conventional treatment of NOCP, but only the American guidelines specify the moment in which it should be used within the conventional drug treatment flow. [8] [9] [10] [2]

Among the policies we looked up, the recommendation of acupuncture for many painful conditions is based on low quality evidence due to the diversity in the methodology of CRCT. [2 8-10] Besides this, such guidelines do not discriminate the power of the recommendation, except for those in Scotland and Canada. [2 8]

Even showing quality, CRCT with adequate randomization and blinding may not provide the best approach for the development of strong evidence base for managing pain, in case the outcomes and its tools are not adequate. [11] Such limitations have been recognized internationally, leading to the development of the Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) in 2002.

The initiative gathered 27 experts from universities, governmental agencies and pharmaceutical industry, who identified consensually a nucleus of six outcome domains that should be considered in CRCT for chronic pain. [12] The outcome domains considered were: (1) pain; (2) physical function; (3) emotional state; (4) evaluation of the participants regarding improvement and satisfaction with treatment; (5) adverse symptoms; and (6) the participant's willingness, but the first four domains listed as main. [13]

The establishment of a standard set of outcome domains in CRCT about chronic pain encourages researchers to consider chronic pain as a complex phenomenon which affects patients in multiple dimensions. It protects against the polarization of selective outcomes, a common problem in all medical literature. It makes systematic reviews and Meta analyses easier, which allows researchers to generate more precise estimations of treatment effects due to sharing common outcomes of individual trials. [14]

Variability in outcome measures in CRCT about NOCP generates inaccuracies in the effectiveness of certain treatments. Although the recommendation of IMMPACT was published in 2003 and updated in 2008, there is no information on whether subsequent clinical trials published comply with IMMPACT recommendations on their outcome measures.

The general aim of this project is to verify whether methodological quality of outcome reporting in published trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes which were executed as of September 2004 when acupuncture was used as a treatment.

METHODS

Study Design

The study comprises a methodological survey of randomized clinical trials which used acupuncture for the treatment of chronic pain. The methodological survey is a type of study on method enquiry, with data collection form selected CRCT, not based on questionnaires but using systematic methods in its execution.

Research question

The question that guides this study was formulated using the PICO strategy, which represents an acronym for Patient, Intervention, Comparison and Outcomes. In evidence-based practice, these four components are the fundamental elements of the research question and the construction of the question for the bibliographic search for evidence. Adequate research question allows the correct definition of what information (evidence) is necessary to solve the clinical research question, maximizes the retrieval of evidence in the databases, focuses the scope of the research and avoids unnecessary searches. [15]

Using the PICO strategy, the question of this survey was: RCT with individuals with Non-Oncologic Chronic Pain (*population*) treated with acupuncture (*intervention*), and where the comparator used was acupuncture sham or not acupuncture (*comparison*), they reported the domains of IMMPACT recommendations (*outcome*).

Reference Sources and Search

All trials already included in CRCT-NOCP, published as of September 2004, selected in the systematic review carried out by Vickers et al. [16] Additional research

will be performed in studies dating as from January 2011 and 6 months before the systematic review of the comprehensive search date on the theme (considering delay in indexing) to nowadays. The search for eligible studies will be accomplished by systematic research of database, namely Lilacs, CINAHL, EMBASE, MEDLINE, AMED, Web of Science, Clinical Trials and Cochrane Central Registry of Controlled Trials, with a defined search strategy, free of idiom restriction.

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For articles published only in summary or for those with important information missing, we will look for complete information about methods and results by contacting the authors.

Two reviewers will be calibrated by the extraction of at least three articles and next, will perform the consensus, in pairs and independently. This procedure shall occur until reviewers are able to extract the data. The collected data will be: name of the first author, date of publication, country of origin, impact of the journal, recruitment date of the first participant, presence of outcome domains IMMPACT, and the tools used for measuring the outcome domains, method of acupuncture, clinical condition of the patient, duration of treatment. Besides this, the study will check if fundamental outcomes are reported by the patient (ORP), if clinical outcomes are reported (COR), if the outcome was reported by a third person (ORT), or a combination of the items above.

The data will be recorded to be transferred to a statistical analysis program later. A regression analysis will be conducted to explore factors that may be associated with the presence of outcome domains according to IMMPACT recommendations.

Risk of Bias

A modified version of Cochrane for risk of bias will be used. [14 17] Reviewers will evaluate the risk of bias for each randomized trial independently, according to the following criteria: generation of random sequence, hiding of the choices, blinding of participants and professionals, blinding of outcome evaluators, if outcomes were reported adequately; incomplete outcomes; selective outcome reporting and other sources of bias. Reviewers will attribute answer alternatives "definitely yes", "probably yes", "probably not" and "definitely not" for each of the domains. [18] Ultimately, "definitely yes" and "probably yes" will be attributed low risk of bias, whereas "definitely not" and "probably not" mean high risk of bias. Reviewers will solve divergences through discussion, and a third person will judge unsolved divergences.

Definitions of IMMPACT outcome domain

The four IMMPACT domains recommended in 2003 and 2008 which will be captured in this study are listed below, together with their definitions

1. Pain: Includes various aspects of pain evaluation (e.g., intensity of pain, duration and frequency). The global evaluation of pain is a general assessment which examines how the pain changed during the treatment.

2. Physical function: refers to the participant's capacity to conduct their daily activities (e.g., tasks, walks, trips and self-care), strength and resistance.

3. Emotional state: refers to the treatment associated to emotional anguish (e.g., depression, anxiety, anger or irritability).

4. Patient's classification of improvement and satisfaction with the treatment: refers to the participant's feeling with the treatment (that is, if they feel the positive features of the treatment surpass the negative ones). This domain overcomes pain classification only.

Thereafter, for each domain, the measurement method is quantized, that is, whether the pain was measured by VAS and / or VAN, whether physical function was measured by multidimensional inventory to pain and / or inventory summary of the pain, whether the emotional state was measured by the Beck depression inventory and /

or mood state profile, and whether the improvement in patient satisfaction was measured by the patient's overall impression of change. The correct applicability of the instrument will also be quantified (if the domain report was executed by the patient, clinical or third parties).

Statistical Analysis

The statistical analyzes carried out in this survey will aim to identify the factors associated with the change in reporting or adherence to the IMMPACT recommendations, in RCT made since its publication.

The descriptive part includes year of publication, place of study, factor of impact of the journal and items of evaluation of methodological quality. These factors will be highlighted as they may influence the adherence of the IMMPACT recommendations. Afterwards, the frequency of measurement of pain, physical function, emotional state and patient satisfaction improvement will be described according to the IMMPACT recommendations.

Compliance with IMMPACT will be measured by the attendance of the four main domains. It is also planned to quantify the number of IMMPACT domains that will be served, in order to generate a score between 0-4 points. The score will be described on average, standard deviation, median and interquartile range.

A score of 0 will be given when the study does not report any of the domains recommended by IMMPACT, score 1, when reporting only one of the recommended domains; Score 2 when reporting two of the recommended domains; Score 3, when reporting three of the recommended domains; and score 4 when reporting the four major domains recommended by IMMPACT.

The factors associated with compliance with the areas of IMMPACT will be investigated. For this, a logistic regression will be performed considering the domains of IMMPACT as dependent variables and the characteristics of the study as independent variables (year of publication, place of study, periodic impact factor and items of methodological quality evaluation). For a good regression analysis, a minimum of 10 references is necessary, which will not be a problem since we will include previous SR studies. The results will be expressed in Odds Ratio with respective 95% confidence intervals.

Factors associated with the IMMPACT score will also be investigated. Depending on the data distribution, analysis of variance (ANOVA) or Kruskal Wallis will be performed. All analyses were 2-sided tests at a significance level of 0.05.

All calculations will run in STATA 14.2.

DISCUSSION

Our survey will evaluate methodologically the outcomes of RCT which used acupuncture for NOCP. We will check whether methodological quality of outcome reporting in published trials have used IMMPACT recommendations in measuring CRCT-NOCP outcomes when acupuncture was used as a treatment. Our survey's outcomes will be significant for public health and for health professionals all over the world, mainly in Brazil.

Since the publication of IMMPACT, it is not known whether studies using acupuncture as an intervention for chronic pain follow IMMPACT's recommendations. Without consistent and more thorough standard outcome reports for patients in CRTC and NOCP, the authors of such studies will be unable to judge objectively the effects of acupuncture. The data compiled on the use of acupuncture will inform both patients and health professionals about its efficacy and safety. Therefore, multiprofessional care and decision-making based on evidence will be made easier.

This Project aims at exploring some hypotheses to determine the use of IMMPACT recommendations on CRTC–NOCP. After the publication of IMMPACT orientations in August 2003 and later, in 2008, CRTC–NOCP which started recruiting participants as from September 2004 had better reports of main outcomes, regarding IMMPACT domains versus journals with lower impact factors. The main domains were reported by the patient, by the clinician, by a third person or by a combination of these subjects.

ETHICS AND DIFUSION

Ethics is not necessary, as this is protocol for a methodological survey. The survey will be published in a journal and presented in congresses with reviews by peers. The evidence of this study will allow health professionals to verify the efficacy and

safety of acupuncture for the treatment of NOCP. Updates of this study should be conducted to inform and orient the practice of health care.

Contributors: LCL is the main researcher who leaded the writing of the manuscript. CCB and LGM are the project manager, co-researcher, who contributed to and writing and review of the manuscript. MTS is co-researcher, and contributed to the writing and review of the manuscript. All the authors have read and approved of the final manuscript.

Acknowledgments: The authors thank Dr. Caio Guimarães for his expert advice.

Sponsorship: This Project has not received any specific funding of any public, private or non-profit agency.

Interest conflict: None.

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Appendix A

Table 1. Search Strategy for database

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 exp Acupuncture Analgesia/
2 exp Acupuncture/
3 acupuncture.mp.
4 1 OR 2 OR 3
5 chronic pain.mp.
6 exp Chronic Pain/
7 exp Chronic Disease/
8 5 OR 6 OR 7
9 4 AND 8

Database: Embase <1974 to 2016 June 28>
Search Strategy:
1 exp acupuncture analgesia/
2 acupuncture.mp.
3 exp acupuncture/
4 1 OR 2 OR 3
5 exp chronic pain/
6 chronic pain.mp.
7 5 OR 6
8 4 AND 7

Database: AMED (Allied and Complementary Medicine) <1985 to June 2016>
Search Strategy:
1 acupuncture.mp.
2 exp Acupuncture/
3 1 OR 2
4 exp Chronic disease/
5 chronic pain.mp.
6 4 OR 5
7 3 AND 6

Database: CINAHL
Search Strategy:
1 (MH "Acupuncture+")
2 (MH "Acupuncture Analgesia")
3 1 OR 2
4 (MH "Chronic Pain")
5 3 AND 4

Database: Cochrane Library
Search Strategy:
1 "acupuncture":ti,ab,kw
2 "acupuncture analgesia":ti,ab,kw

3 1 OR 2
4 "chronic pain":ti,ab,kw
5 3 AND 4

Database: Web of Science <1976 to July 2016>
Search Strategy:
1 acupuncture
2 *acupuncture*
3 1 OR 2
4 chronic pain
5 chronic *pain*
6 4 OR 5
7 3 AND 6

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract			not applicable
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		☐	not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		10
Sponsor	5b	Provide name for the review funder and/or sponsor		☐	not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		☐	not applicable
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐		5

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		5, 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		5, 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐		5, 6
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐		7
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		8, 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐		8, 9
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐		9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		9

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		7, 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		☐	not applicable