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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026524
Article Type:	Protocol
Date Submitted by the Author:	06-Sep-2018
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Keywords:	Clown intervention, Symptom management, Symptom clusters, Child, Adolescent, Pediatrics

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A SYSTEMATIC REVIEW PROTOCOL EXAMINING THE EFFECTIVENESS OF HOSPITAL CLOWNS FOR SYMPTOM CLUSTER MANAGEMENT IN PEDIATRICS

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Acknowledgements
We would like to thank the Coordination of Improvement of Higher Education Personnel - CAPES, Brazil, for supporting this research with regular doctoral scholarship to Luís Carlos Lopes Júnior as well as his Doctoral Fellowship/Internship at the University of Alberta (UofA), Edmonton, Alberta, Canada, through the Doctoral "Sandwich" Program Abroad – PDSE/CAPES (Process Nº: BEX 9321/14-4).
Author Contributions: LCLJ, RAGL and KO conceptualized and designed the protocol, drafted the initial manuscript, and reviewed the manuscript. LCLJ, EB and ETN defined the concepts and search items, data extraction process as well as methodological appraisal of the studies. DSCS and MDRN planned the data extraction and statistical analysis. LCN and GPS, provided critical insights. All authors have approved and contributed to the final written manuscript.
Funding: This research was funded by the Coordination for the Improvement of Higher Education Personnel (CAPES), Process number: BEX 9321/14-4.
Data Statement section: PROSPERO registration number: CRD42018107099. Available in: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=107099

Word Count: 2058 words.
Disclaimer: The views of the authors do not necessarily reflect those of the NHS, NIHR or the Department of Health.
Competing interests: None declared.
Patient consent: Not required.
Provenance and peer review: Not commissioned; externally peer reviewed.

ABSTRACT

Introduction: Clown intervention may playing an important complementary role in pediatric care and recovery. However, data on its utility for symptom cluster management of hospitalized children and adolescents in acute and chronic disorders are yet to be critically evaluated. As clinicians strive to minimize the psychological burden during hospitalization, it is important that they are aware of the scientific evidences available regarding clown intervention for symptom management. We aim to provide quality evidence for the effectiveness of clown intervention on symptom cluster management in pediatric inpatients, both in acute and chronic conditions.

Methods and analysis: A systematic review of randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs) will be conducted. MEDLINE, Web of Science, Cochrane Library, Science Direct, PsycINFO, CINAHL, LILACS and SciELO databases will be searched from January 2000 to December 2018. Primary outcomes will include measures related with the effect of clown intervention on symptom cluster of pediatric inpatients (anxiety, pain, stress, and psychological, emotional responses and perceived well-being). Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the methodological appraisal of the studies will be assessed by the Jadad Scale as well as Cochrane Risk-of-Bias Tool for RCTs, and Risk-of-Bias In Non-Randomized Studies-ROBINS-I Tool for NRCTs. A narrative synthesis will be conducted for all included studies. Also, if sufficient data are available, a meta-analysis will be conducted. The effect sizes will be generated using Hedges' g score, for both fixed and random effect models. I^2 statistics will be used to assess heterogeneity and identify their potential sources.

Ethics and dissemination: As it will be a systematic review, without human beings involvement, there will be no require for ethical approval. Findings will be disseminated widely through peer-reviewed publication and in various media, e.g. conferences, congresses or symposia.

PROSPERO registration number: CRD42018107099.

Keywords: Clown intervention; Symptom management; Symptom clusters; Child; Adolescent; Pediatrics.

Strengths and limitations of this study:

- This protocol reduces the possibility of duplication, gives transparency to the methods and processes that will be used, reduces possible biases and allows peer review.
- Will offer highest level of evidence for informed decisions from this systematic review of randomised controlled trials as well as non-randomized controlled trials.
- This systematic review will be the first to explore the effectiveness of clown intervention for symptom cluster management of hospitalized children and adolescents in acute and chronic disorders.
- The scarcity of of randomised controlled trials undertaken with pediatric inpatients with chronic disorders, the publication bias and the methodological quality of the grey literature found may be the main limitations of the study.

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INTRODUCTION

Illness produces stress, and well-being, self-confidence, and psychological processes that may regulate immune responses can be significant factors for recovery and response to treatment.[1,2] The procedures and treatments performed in hospital settings can further increase patient burden, especially for hospitalized children and adolescents, requiring specific strategies to help them cope with hospitalization, avoid stress-related disorders, and psychoneurological symptom clusters.[2–7] Therefore, alleviating psychoneurological symptom clusters caused by the hospitalization process has become of major interest in pediatric wards.[8–17] Since therapeutic clowning began in North America in 1986, it has become a popular practice in pediatric settings, mainly in acute and rehabilitation hospitals worldwide.[18,19] As clown intervention, a non-pharmacological approach, has been shown to have a positive effect in the outcomes of pediatric patients[18–20] it is increasingly thought to play an important complementary role in health care by easing the recovery of these patients.[18,20]

It has been shown that this intervention can enhance emotional and behavioral processes, for instance, improving well-being and self-confidence, and reducing stress and anxiety levels.[21–29] In addition, evidence suggests that hospital clowns help pediatric patients to better adapt to their hospital surroundings and can distract from, and demystify painful or frightening procedures through 'doses of fun' to complement traditional clinical interventions.[18,24,27] This hypothesis is supported by studies showing that clown intervention enhances emotional and behavioral responses.[22,23] Positive changes in emotional responses arising from humor and laughter have been correlated with increased pain thresholds and immunity, inversely correlated with stress hormone levels, and linked to positive health.[22,23] Despite this recognition, few studies have investigated the molecular mechanisms that mediate the positive health outcomes of clown intervention.[30–33]

Recently, two systematic reviews and meta-analyses looked at the effects of clown intervention in pediatric hospital settings.[34,35] One of them concluded that hospital clowns play a significant role in reducing stress and anxiety levels in children staying in a pediatric ward or undergoing invasive procedures or minor surgeries under anesthesia, as well as in their parents[34] and the other confirmed the strong effect of clown intervention in reducing children's pre-operative psychological distress.[35] However, both reviews focused solely on

acute situations. Furthermore, one of the reviews[34] looked at both randomized and non-randomized controlled trials, but lacked a specific tool for a bias analysis of the latter. Finally, both failed to investigate the effectiveness of clown intervention for a range of symptom clusters in hospitalized children and adolescents in depth. Hence, in this systematic review we evaluated evidence on the effectiveness of clown intervention for symptom clusters management in hospitalized children and adolescents in a variety of pediatric settings, both in acute and chronic conditions, from both randomized and nonrandomized controlled trials, assessing the quality of the latter with a recently developed tool, ROBINS-1.[36]

This review will expand on the above-mentioned works, in order to identify recent methodological and scientific progress until December 2018. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist as guidance,[37] we propose a systematic and reproducible strategy to query the literature about the effectiveness of clown intervention on symptom cluster management in pediatric inpatients.

METHODS AND ANALYSIS

Search Strategy

The search strategy will be performed using resources that enhance methodological transparency and improve the reproducibility of the results and evidence synthesis. In this sense, the search strategy will be elaborated and implemented prior to study selection, according to the PRISMA-P checklist as guidance.[37] Additionaly, using the PICOS strategy[38] we elaborated the guiding question of this review, in order to ensure the systematic search of available literature: *"What is the effect of clown intervention for symptom management in hospitalized children and adolescents?"* The PROSPERO – International Prospective Register of Systematic Reviews – registration number is: CRD42018107099 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=107099)

Studies will be retrieved using eight databases: MEDLINE (via Pubmed), Web of Science, Cochrane Library, Science Direct, PsycINFO, CINAHL, LILACS and SciELO. In order to reflect contemporary practice, a search of the literature from the last 18 years (January 2000 to December 2018) will be performed. Language restrictions will be applied and only articles in English will be included. In addition, the reference section in the studies returned by the above search were scrutinized for additional relevant articles. It is noteworthy that two researchers (LCLJ and EOB) will performed the search strategy independently. Also,

the bibliographic software EndNote (https://www.myendnoteweb.com/) will be used to store, organize, and manage all the references and ensure a systematic and comprehensive search.

Initially, the existence of controlled descriptors (such as MeSH terms, CINAHL headings, PsycINFO thesaurus, and DeCS-Health Science Descriptors) and their synonyms (key words) was verified in each database. The search terms were combined using the Boolean operators "AND" and "OR".[39]

Subsequently, a search strategy combining MeSH terms and free-text words, such as: (child OR child, hospitalized OR adolescent OR adolescent, hospitalized OR pediatrics) AND (clown doctors OR clown intervention OR clowns OR therapeutic clown OR clowns in hospital) AND (symptoms OR affective symptoms OR behavioral symptoms OR clusters of neuropsychological symptoms OR neuropsychological symptoms OR anxiety OR stress, psychological OR distress OR psychological impact) was used. In order to locate the clinical trials, we added a filter after the PICOS search strategy that included the following terms: AND (randomized controlled trial OR randomized controlled trials as topic OR controlled clinical trial OR clinical trial OR nonrandomized controlled trials).

Study selection criteria

A summary of the participants, interventions, comparators and outcomes considered, as well as the type of studies included according to PICOS strategy, is provided in Table 1.

Table 1 Inclusion and exclusion criteria

PICOS Strategy[38]	**Inclusion criteria**	**Exclusion criteria**
P – Population	Hospitalized children and adolescents for acute conditions or chronic disorders.	Non-hospitalized children and adolescents as well as presence of *coulrophobia*.
I – Intervention	Clown intervention	
C – Comparison	Usual standard of care without receiving clown intervention.	
O – Outcome	Any measure related to symptom clusters: anxiety, pain, stress, and psychological, emotional responses and perceived well-being.	Studies that do not report any symptom as primary outcome
S – Study design	Randomized controlled trial and nonrandomized controlled trials (quasi-experimental study).	All the non-primary literature, such as reviews, dissertations, theses, editorials, protocol studies and clinical guidelines.

Screening and data extraction

Initial screening of studies will be based on the information contained in their titles and abstracts and will be conducted by two independent investigators (LCLJ and EOB). When the reviewers disagreed, the article will be reevaluated and, if the disagreement persisted, a

third reviewer (ETN) will make a final decision. Full-paper screening will be conducted by the same independent investigators. Cohen's kappa will be used to measure inter-coder agreement in each screening phase.

Data will be extracted using a previously proposed tool[3], including four domains: i) identification of the study (article title; journal title; impact factor of the journal; authors; country of the study; language; publication year; host institution of the study [hospital; university; research center; single institution; multicenter study]); ii) methodological characteristics (study design; study objective or research question or hypothesis; sample characteristics, e.g. sample size, sex; age, race; acute and/or chronic diagnoses; groups and controls; stated length of follow-up; validated measures; statistical analyses, adjustments; iii) main findings; and iv) conclusions. If the outcome data in the original article were unclear, the corresponding author will be contacted via e-mail for clarification. For data extraction two independent Microsoft Excel spreadsheets will elaborated for two reviewers (LCLJ and EOB) to summarize the data from the included studies. Then, the spreadsheets were combined into one. Disagreements will be resolved by a third investigator (ETN).

Quality assessment

Methodological quality of the RCTs will be assessed using the Jadad scale,[40] a widely used tool for classification of the quality of the evidence from RCTs. The Jadad scale scores range from 0 to 5, with studies scoring < 3 considered as low quality, and studies that score ≥ 3 classified as high quality.[40] The internal validity and risk of bias for RCTs will be assessed with the appraisal tool from the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0,[41] which assesses the following study-level aspects: (1) randomisation sequence allocation; (2) allocation concealment; (3) blinding; (4) completeness of outcome data and (5) selective outcome reporting; and classifies studies into low, high or unclear risk of bias. For assessing NRCT, the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I), a recently developed tool, will be used.[36] ROBINS-I is particularly useful to those undertaking systematic reviews that include non-randomized studies of interventions. This tool is guided through seven chronologically arranged bias domains (pre-intervention, at intervention, and post-intervention), and the interpretations of domain-level and overall risk of bias judgment in ROBINS-I are classified in low, moderate, serious, or critical risk of bias.[36]

Two independent reviewers (LCLJ, EOB) will assess the methodological quality of eligible trials. Two independent reviewers will score the selected studies and disagreements will be resolved by a third reviewer (ETN). The risk of bias for each outcome across

individual studies will be summarized as a narrative statement, and supported by a risk of bias table. A review-level narrative summary of the risk of bias will also be provided.

Descriptive analysis and meta-analysis

For studies with a high or unclear risk of bias, defined as high or nuclear risk in 50% or more of the quality assessment outcomes, a narrative description of the risk of bias will be provided. Risk of Bias assessments will be incorporated into synthesis by performing sensitivity analysis (i.e., limiting to studies at lowest risk of bias in a secondary analysis).

A narrative synthesis will be conducted for all the included studies. Whenever possible, continuous and dichotomous outcomes will be pooled together for meta-analysis purposes. All effect sizes will be transformed into a common metric, in order to make them comparable across studies – the bias-corrected standardised difference in means (Hedges' g) – classified as positive when in favour of the intervention and negative when in favour of the control. Heterogeneity will be assessed using I^2.[42] The presence of publication bias will be evaluated by use of a funnel plot and the Duval and Tweedie's trim and fill method.[43]

Patient and public involvement, ethics and dissemination

Patients were not directly involved in the design of this study. As this is a protocol for a systematic review and no participant recruitment will take place, their involvement on the recruitment and dissemination of findings to participants was not applicable. In addition, any amendments to this protocol will be documented with reference to saved searches and analysis methods, which will be recorded in bibliographic databases (Ovid), EndNote and Excel templates for data collection and synthesis.

The results of the review will be disseminated in an open access journal to ensure access for undergraduate and graduate students, researchers, academics and research groups and also will be disseminated in various media, such as: conferences, seminars, congresses or symposia.

DISCUSSION

One of the strengths of the proposed study is to apply a reproducible and transparent procedure for systematic review of the literature. In this protocol, we clearly describe the types of studies, participants, interventions and outcomes that will be included, as well as the data sources, search strategy, data extraction methods (including quality assessment) and methods of combining data.[44] By publishing the research protocol, we reinforce the clarity of

the strategy and minimise the risk of bias, namely selective outcome reporting.[41] Second, we will focus solely on the impact of the the effectiveness of clown intervention on symptom cluster management in pediatric inpatients. This results shall provide high-level information to inform, support and customise decisions from the clinicians in pediatrics settings.

Potential limitations of this study include the heterogeneity of measures and outcomes evaluated and the potentially reduced number of studies in subgroup analyses, which may negatively influence the statistical power in data synthesis.

As clinicians strive to minimize the psychological burden during the hospitalization process, they must be aware of the scientific evidence available to help them incorporate appropriate laughter and play to clinical practice.[18] Children and adolescents who require hospitalization represent a special challenge for the health care system as well as for health professionals, both because of the illness itself and because of the treatment process.[13,32,33] In addition, hospitalized children and adolescents with acute or chronic disorders are also stressed by the separation from their parents, by the hospital environment, by the fear of painful treatments or by the uncertainty in the treatment outcome.[20] This review will demonstrated the value in the involvement of the hospital clowns for symptom cluster management in pediatric inpatients.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
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	n/a
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
	#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	n/a

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4 and 5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4 and 5
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	4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4 and 5
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
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	6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7
	#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 (such as I2, Kendall's τ)	7
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7 and 8

A SYSTEMATIC REVIEW PROTOCOL EXAMINING THE EFFECTIVENESS OF HOSPITAL CLOWNS FOR SYMPTOM CLUSTER MANAGEMENT IN PEDIATRICS

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026524.R1
Article Type:	Protocol
Date Submitted by the Author:	19-Nov-2018
Complete List of Authors:	LOPES-JÚNIOR, LUÍS CARLOS; Universidade de Sao Paulo Campus de Ribeirao Preto, Department Maternal-Infant Nursing and Public Health Lima, Regina Aparecida Garcia; Universidade de Sao Paulo Campus de Ribeirao Preto, Department of Maternal-Infant and Public Health Nursing Olson, Karin; University of Alberta, Faculty of Nursing Bomfim, Emiliana; University of Saskatchewan College of Medicine, Department of Medicine Neves, Eliane Tatsch; Universidade Federal de Santa Maria, Nursing Department Silveira, Denise Sayuri Calheiros da; Universidade de Sao Paulo Faculdade de Medicina de Ribeirao Preto, Department of Biochemistry and Immunology Nunes, Michelle Darezzo Rodrigues; Faculdade de Enfermagem da UERJ, Nursing Department Nascimento, Lucila; University of São Paulo, Department of Maternal-Infant and Public Health Nursing Pereira-da-Silva, Gabriela; Universidade de Sao Paulo Campus de Ribeirao Preto, Department of Maternal-Infant and Public Health Nursing
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Paediatrics, Complementary medicine, Evidence based practice, Research methods
Keywords:	Clown intervention, Symptom management, Symptom clusters, Child, Adolescent, Pediatrics

Title Page – BMJ Open

A SYSTEMATIC REVIEW PROTOCOL EXAMINING THE EFFECTIVENESS OF HOSPITAL CLOWNS FOR SYMPTOM CLUSTER MANAGEMENT IN PEDIATRICS

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Acknowledgements
We would like to thank the Coordination of Improvement of Higher Education Personnel - CAPES, Brazil, for supporting this research with regular doctoral scholarship to Luís Carlos Lopes Júnior as well as his Doctoral Fellowship/Internship at the University of Alberta (UofA), Edmonton, Alberta, Canada, through the Doctoral "Sandwich" Program Abroad – PDSE/CAPES (Process Nº: BEX 9321/14-4).
Author Contributions: LCLJ, RAGL and KO conceptualized and designed the protocol, drafted the initial manuscript, and reviewed the manuscript. LCLJ, EB and ETN defined the concepts and search items, data extraction process as well as methodological appraisal of the studies. DSCS and MDRN planned the data extraction and statistical analysis. LCN and GPS, provided critical insights. All authors have approved and contributed to the final written manuscript.
Funding: This research was funded by the Coordination for the Improvement of Higher Education Personnel (CAPES), Process number: BEX 9321/14-4.
Data Statement section: PROSPERO registration number: CRD42018107099. Available in: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=107099

Word Count: 2446 words.
Disclaimer: The views of the authors do not necessarily reflect those of the NHS, NIHR or the Department of Health.
Competing interests: None declared.
Patient consent: Not required.
Provenance and peer review: Not commissioned; externally peer reviewed.

ABSTRACT

Introduction: Clown intervention may playing an important complementary role in pediatric care and recovery. However, data on its utility for symptom cluster management of hospitalized children and adolescents in acute and chronic disorders are yet to be critically evaluated. As clinicians strive to minimize the psychological burden during hospitalization, it is important that they are aware of the scientific evidences available regarding clown intervention for symptom management. We aim to provide quality evidence for the effectiveness of clown intervention on symptom cluster management in pediatric inpatients, both in acute and chronic conditions.

Methods and analysis: A systematic review of randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs) will be conducted. MEDLINE, Web of Science, Cochrane Library, Science Direct, PsycINFO, CINAHL, LILACS and SciELO databases will be searched from January 2000 to December 2018. Primary outcomes will include measures related with the effect of clown intervention on symptom cluster of pediatric inpatients (anxiety, depression, pain, fatigue, stress, and psychological, emotional responses and perceived well-being). Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the methodological appraisal of the studies will be assessed by the Jadad Scale as well as Cochrane Risk-of-Bias Tool for RCTs, and Risk-of-Bias In Non-Randomized Studies-ROBINS-I Tool for NRCTs. A narrative synthesis will be conducted for all included studies. Also, if sufficient data are available, a meta-analysis will be conducted. The effect sizes will be generated using Hedges' g score, for both fixed and random effect models. I^2 statistics will be used to assess heterogeneity and identify their potential sources.

Ethics and dissemination: As it will be a systematic review, without human beings involvement, there will be no require for ethical approval. Findings will be disseminated widely through peer-reviewed publication and in various media, e.g. conferences, congresses or symposia.

PROSPERO registration number: CRD42018107099.

Keywords: Clown intervention; Symptom management; Symptom clusters; Child; Adolescent; Pediatrics.

Strengths and limitations of this study:

- This protocol reduces the possibility of duplication, gives transparency to the methods and processes that will be used, reduces possible biases and allows peer review.
- Will offer highest level of evidence for informed decisions from this systematic review of randomised controlled trials as well as non-randomized controlled trials.
- This systematic review will be the first to explore the effectiveness of clown intervention for symptom cluster management of hospitalized children and adolescents in acute and chronic disorders.
- The scarcity of of randomised controlled trials undertaken with pediatric inpatients with chronic disorders, the publication bias and the methodological quality of the grey literature found may be the main limitations of the study.

A SYSTEMATIC REVIEW PROTOCOL EXAMINING THE EFFECTIVENESS OF HOSPITAL CLOWNS FOR SYMPTOM CLUSTER MANAGEMENT IN PEDIATRICS

INTRODUCTION

Illness produces stress, and well-being, self-confidence, and psychological processes that may regulate immune responses can be significant factors for recovery and response to treatment.[1,2] The procedures and treatments performed in hospital settings can further increase patient burden, especially for hospitalized children and adolescents, requiring specific strategies to help them cope with hospitalization, avoid stress-related disorders, and psychoneurological symptom clusters.[2–7] Therefore, alleviating psychoneurological symptom clusters caused by the hospitalization process has become of major interest in pediatric wards.[8–17] Since therapeutic clowning began in North America in 1986, it has become a popular practice in pediatric settings, mainly in acute and rehabilitation hospitals worldwide.[18,19] As clown intervention, a non-pharmacological approach, has been shown to have a generally positive effect in the outcomes of pediatric patients[18–20], reviews conducted in on this theme showed conflicting results.[21–23]

It has been shown that this intervention can enhance emotional and behavioral processes, for instance, improving well-being and self-confidence, and reducing stress and anxiety levels.[24–32] In addition, evidence suggests that hospital clowns help pediatric patients to better adapt to their hospital surroundings and can distract from, and demystify painful or frightening procedures through 'doses of fun' to complement traditional clinical interventions.[18,27,30] This hypothesis is supported by studies showing that clown intervention enhances emotional and behavioral responses.[25,26] Positive changes in emotional responses arising from humor and laughter have been correlated with increased pain thresholds and immunity, inversely correlated with stress hormone levels, and linked to positive health.[25,26] Despite this recognition, few studies have investigated the molecular mechanisms that mediate the positive health outcomes of clown intervention.[33–36]

Recently, a review of literature has investigated evidences from the 28 randomized controlled trials (RCTs) for the effects of healthcare clowning on children. This review revealed different settings in which RCTs have been conducted such as preoperative areas, during medical procedures, and during hospitalization. Overall, the results show that clown interventions are effective in decreasing negative emotions and psychological symptoms and in enhancing the well-being of patients and their relatives.[23]

Additionally, two systematic reviews and meta-analyses looked at the effects of clown intervention in pediatric hospital settings.[21,22] One of them concluded that hospital clowns play

a significant role in reducing stress and anxiety levels in children staying in a pediatric ward or undergoing invasive procedures or minor surgeries under anesthesia, as well as in their parents[21] and the other confirmed the strong effect of clown intervention in reducing children's pre-operative psychological distress.[22] However, both reviews focused solely on acute situations. Furthermore, one of the reviews[21] looked at both randomized and non-randomized controlled trials, but lacked a specific tool for a bias analysis of the latter. Finally, both failed to investigate the effectiveness of clown intervention for a range of symptom clusters in hospitalized children and adolescents in depth. Hence, in this systematic review we evaluated evidence on the effectiveness of clown intervention for symptom clusters management in hospitalized children and adolescents in a variety of pediatric settings, both in acute and chronic conditions, from both randomized and nonrandomized controlled trials, assessing the quality of the latter with a recently developed tool, ROBINS-1.[37]

This review will expand on the above-mentioned works, in order to identify recent methodological and scientific progress until December 2018. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist as guidance,[38] we propose a systematic and reproducible strategy to query the literature about the effectiveness of clown intervention on symptom cluster management in pediatric inpatients.

METHODS AND ANALYSIS

Search Strategy

The search strategy will be performed using resources that enhance methodological transparency and improve the reproducibility of the results and evidence synthesis. In this sense, the search strategy will be elaborated and implemented prior to study selection, according to the PRISMA-P checklist as guidance.[38] Additionally, using the PICOS strategy[39] we elaborated the guiding question of this review, in order to ensure the systematic search of available literature: *"What is the effect of clown intervention for symptom management in hospitalized children and adolescents?"* The PROSPERO – International Prospective Register of Systematic Reviews – registration number is: CRD42018107099 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=107099)

Studies will be retrieved using eight databases: MEDLINE (via Pubmed), Web of Science, Cochrane Library, Science Direct, PsycINFO, CINAHL, LILACS and SciELO. In order to reflect contemporary practice, a search of the literature from the last 18 years (January 2000 to December 2018) will be performed. There will be no restriction regarding the language

to avoid the reduce the yield of appropriate articles and also generalizability. In addition, the reference section in the studies returned by the above search were scrutinized for additional relevant articles. It is noteworthy that two researchers (LCLJ and EOB) will performed the search strategy independently. Also, the bibliographic software EndNote (https://www.myendnoteweb.com/) will be used to store, organize, and manage all the references and ensure a systematic and comprehensive search.

Initially, the existence of controlled descriptors (such as MeSH terms, CINAHL headings, PsycINFO thesaurus, and DeCS-Health Science Descriptors) and their synonyms (key words) was verified in each database. The search terms were combined using the Boolean operators "AND" and "OR".[40]

Subsequently, a search strategy combining MeSH terms and free-text words, such as: (child OR child, hospitalized OR adolescent OR adolescent, hospitalized OR pediatrics) AND (clown doctors OR medical clown OR clown intervention OR clowns OR therapeutic clown OR clowns in hospital) AND (symptoms OR affective symptoms OR behavioral symptoms OR clusters of neuropsychological symptoms OR neuropsychological symptoms OR anxiety OR stress, psychological OR distress OR psychological impact) was used. In order to locate the clinical trials, we added a filter after the PICOS search strategy that included the following terms: AND (randomized controlled trial OR randomized controlled trials as topic OR controlled clinical trial OR clinical trial OR nonrandomized controlled trials).

Study selection criteria

A summary of the participants, interventions, comparators and outcomes considered, as well as the type of studies included according to PICOS strategy, is provided in Table 1.

Table 1 Inclusion and exclusion criteria

PICOS Strategy[39]	**Inclusion criteria**	**Exclusion criteria**
P – Population	Hospitalized children and adolescents for acute conditions or chronic disorders.	Non-hospitalized children and adolescents.
I – Intervention	Clown intervention	
C – Comparison	Usual standard of care without receiving clown intervention.	
O – Outcome	Any measure related to symptom clusters: anxiety, depression, pain, fatigue, stress, and psychological, emotional responses and perceived well-being.	Studies that do not report any symptom cluster as primary outcome
S – Study design	Randomized controlled trial and nonrandomized controlled trials (quasi-experimental study).	All the non-primary literature, such as reviews, dissertations, theses, editorials, protocol studies and clinical guidelines.

Symptom clusters outcomes will be measured all three dimensions of symptom occurrence, severity, and distress.[41] The key outcome will be measured considering the extent of symptom cluster felt by children during the hospitalization.

The primary outcome measures will be the number of children with any symptom cluster during hospitalization, the extent of symptom cluster felt by children measured by any validated scale for the respective symptoms. The secondary outcome measures will be the number of children with acute conditions or chronic disorders, number of children satisfied with the care provided, number of parents satisfied with the care provided.

It is noteworthy that symptom cluster composition, consistency, and stability vary widely depending on a host of measurement factors, including the optimal assessment tool (long vs. short), the most clinically relevant symptom dimensions (prevalence vs. severity or distress caused), the optimal analytical method to derive the cluster, the optimal statistical ‘‘cutoff’’ points to define symptom cluster, and the optimal timing of assessment.[41] Thus, we will consider in our analysis factors such as variation in measurement timing, the number of symptoms included in an analysis, in order to generalizability of symptom cluster over time.[42,43]

Screening and data extraction

Initial screening of studies will be based on the information contained in their titles and abstracts and will be conducted by two independent investigators (LCLJ and EOB). When the reviewers disagreed, the article will be reevaluated and, if the disagreement persisted, a third reviewer (ETN) will make a final decision. Full-paper screening will be conducted by the same independent investigators. Cohen’s kappa will be used to measure inter-coder agreement in each screening phase.

Data will be extracted using a previously proposed tool[44], including four domains: i) identification of the study (article title; journal title; impact factor of the journal; authors; country of the study; language; publication year; host institution of the study [hospital; university; research center; single institution; multicenter study]); ii) methodological characteristics (study design; study objective or research question or hypothesis; sample characteristics, e.g. sample size, sex; age, race; acute and/or chronic diagnoses; groups and controls; stated length of follow-up; validated measures; statistical analyses, adjustments; iii) main findings; and iv) conclusions. If the outcome data in the original article were unclear, the corresponding author will be contacted via e-mail for clarification. For data extraction two independent Microsoft Excel spreadsheets will elaborated for two reviewers (LCLJ and EOB)

to summarize the data from the included studies. Then, the spreadsheets were combined into one. Disagreements will be resolved by a third investigator (ETN).

Quality assessment

Methodological quality of the RCTs will be assessed using the Jadad scale,[45] a widely used tool for classification of the quality of the evidence from RCTs. The Jadad scale scores range from 0 to 5, with studies scoring < 3 considered as low quality, and studies that score ≥ 3 classified as high quality.[45] The internal validity and risk of bias for RCTs will be assessed with the appraisal tool from the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0,[46] which assesses the following study-level aspects: (1) randomisation sequence allocation; (2) allocation concealment; (3) blinding; (4) completeness of outcome data and (5) selective outcome reporting; and classifies studies into low, high or unclear risk of bias. For assessing NRCT, the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I), a recently developed tool, will be used.[37] ROBINS-I is particularly useful to those undertaking systematic reviews that include non-randomized studies of interventions. This tool is guided through seven chronologically arranged bias domains (pre-intervention, at intervention, and post-intervention), and the interpretations of domain-level and overall risk of bias judgment in ROBINS-I are classified in low, moderate, serious, or critical risk of bias.[37]

Two independent reviewers (LCLJ, EOB) will assess the methodological quality of eligible trials. Two independent reviewers will score the selected studies and disagreements will be resolved by a third reviewer (ETN). The risk of bias for each outcome across individual studies will be summarized as a narrative statement, and supported by a risk of bias table. A review-level narrative summary of the risk of bias will also be provided.

Descriptive analysis and meta-analysis

For studies with a high or unclear risk of bias, defined as high or nuclear risk in 50% or more of the quality assessment outcomes, a narrative description of the risk of bias will be provided. Risk of Bias assessments will be incorporated into synthesis by performing sensitivity analysis (i.e., limiting to studies at lowest risk of bias in a secondary analysis).

A narrative synthesis will be conducted for all the included studies. All effect sizes will be transformed into a common metric, in order to make them comparable across studies – the bias-corrected standardised difference in means (Hedges' g) – classified as positive when in favour of the intervention and negative when in favour of the control. For continuous outcome measures, standardized mean diferences (SMD) and risk ratio (RR) for categorical outcomes

will be considered for the final assessment from individual studies. SMD was chosen as a measure of pooled results considering the likely variability in the measuring scales for continuous outcomes.[21] The SMD will be categorized as small, medium, and large based on the thresholds 0.2, 0.5, and 0.8, respectively, as suggested by Cohen's.[47] The 95 % CI will be used to represent the deviation from the point estimate for both the individual studies and the pooled estimate. Heterogeneity between the studies will be assessed using forest plot visually, as well as I^2 statistics.[48] Random effect models will be used in case of moderate to severe heterogeneity otherwise fixed effect models will be generated. In addition, the presence of publication bias will be evaluated by use of a funnel plot and the Duval and Tweedie's trim and fill method.[49]

Patient and public involvement

Patients were not directly involved in the design of this study. As this is a protocol for a systematic review and no participant recruitment will take place, their involvement on the recruitment and dissemination of findings to participants was not applicable.

Amendments

Any amendments to this protocol will be documented with reference to saved searches and analysis methods, which will be recorded in bibliographic databases (Ovid), EndNote and Excel templates for data collection and synthesis.

Dissemination

The results of the review will be disseminated in an open access journal to ensure access for undergraduate and graduate students, researchers, academics and research groups and also will be disseminated in various media, such as: conferences, seminars, congresses or symposia.

DISCUSSION

One of the strengths of the proposed study is to apply a reproducible and transparent procedure for systematic review of the literature. In this protocol, we clearly describe the types of studies, participants, interventions and outcomes that will be included, as well as the data sources, search strategy, data extraction methods (including quality assessment) and methods of combining data.[50] By publishing the research protocol, we reinforce the clarity of the strategy and minimise the risk of bias, namely selective outcome reporting.[46] Second, we will focus solely on the impact of the the effectiveness of clown intervention on symptom cluster

management in pediatric inpatients. This results shall provide high-level information to inform, support and customise decisions from the clinicians in pediatrics settings.

Potential limitations of this study include the heterogeneity of measures and outcomes evaluated and the potentially reduced number of studies in subgroup analyses, which may negatively influence the statistical power in data synthesis.

As clinicians strive to minimize the psychological burden during the hospitalization process, they must be aware of the scientific evidence available to help them incorporate appropriate laughter and play to clinical practice.[18] Children and adolescents who require hospitalization represent a special challenge for the health care system as well as for health professionals, both because of the illness itself and because of the treatment process.[13,35,36] In addition, hospitalized children and adolescents with acute or chronic disorders are also stressed by the separation from their parents, by the hospital environment, by the fear of painful treatments or by the uncertainty in the treatment outcome.[20] This review will demonstrated the value in the involvement of the hospital clowns for symptom cluster management in pediatric inpatients.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
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	n/a
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
	#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	n/a

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4 and 5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4 and 5
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	4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4 and 5
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
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	6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7
	#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 (such as I2, Kendall's τ)	7
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7 and 8