Author's response to reviews

Title: Process of care in outpatient Integrative healthcare facilities: a systematic review of clinical trials.

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Author's response to reviews: see over
Dear Dr Giray,

Re: Response to Reviewers Comments for Manuscript ID: 1733569878117742

Thank you for reviewing this manuscript and providing valuable feedback. Please find below our responses in blue to the reviewers comments. All changes made to the manuscript uploaded today have been performed using track changes so you can easily identify the amendments.

**Reviewer #1 Comments**

This paper addresses an important topic and contributes to moving integrative health care from simply being conceptualised as to its nature to being evaluated for its effectiveness. Consistency in the use of terminology and clear definitions for the terms used in this paper will greatly enhance its intelligibility.

We thank the reviewer for their comments. We have aimed to include definitions and consistency in terms throughout the paper.

**Major essential revisions**

1. The title and abstract refer to a systematic review of ‘all controlled clinical trials of the process of care in outpatient integrative healthcare facilities’. However, this description is at odds with that in the Methods which refers to a systematic review of clinical trials integrating conventional and complementary medicine practitioners in a shared context to administer an individualized treatment plan’. Alignment of the title, aim described in the Abstract, aim in the Methods section, and presentation of the results is required.

We have amended the abstract as follows: “We sought to review the outcomes of recent clinical trials, explore the design of the interventions and to discuss the methodological approaches and issues that arise when investigating a complex mix of interventions in order to guide future research”. This aligns more closely with the Introduction where we have articulated the objectives as:

“…our review has three primary objectives:

1. To systematically review the quality and outcomes of clinical trials of IHC
2. To explore the design of IHC interventions, including process of care
3. To review research methodology employed in IHC clinical trials
2. Introduction

The last line of the first paragraph refers to ‘whole system interventions’. This term needs to be clearly defined. (Later, in the Discussion on p14, the authors refer to whole system practitioners’)

In the first paragraph we have deleted the reference to ‘whole system interventions’ and replaced it with ‘multidisciplinary complex interventions’ which more accurately describes IHC.

A future reference to ‘whole system’ in the discussion has been replaced with “Bell argues that the whole therapeutic strategy of IHC needs to be evaluated.”

We then go on to define ‘whole system interventions’ in the discussion as follows:

“Whole systems can be defined as “approaches to healthcare in which practitioners apply bodies of knowledge and associated practices in order to maximize the patients’ capacity to achieve mental and physical balance and restore their own health, using individualised, non-reductionist approaches to diagnosis and treatment”[76]. In the case of IHC, it is the individualised integrative therapeutic strategy that is the whole system intervention.”

We have removed the reference to “whole system practitioners”.

A definition of integrative health care is offered in the first paragraph: ‘where conventional and complementary medicine practitioners collude in patient care’. The second paragraph then goes on to discuss a number of different definitions. It would be more useful for the reader if discussions of definitions are collated.

We have removed the definition from the opening paragraph. We have combined our discussion on the definition of integrative healthcare as follows:

“IHC splinter off when the structure and process of care are considered. For example, IHC may refer to the process of patient care where allopathic and CM clinicians work as a team. The “team” may operate in a multi-disciplinary or inter-disciplinary way, or through a democratic referral system or perhaps with the allopathic physician as the gatekeeper and the CM practitioner as adjunct practitioner [17-19]. Further confusion is added to the typology of this field by regional variations, where “integrated” is used in the UK and parts of Europe, in the same way in which “integrative” is used in the US and Australia.

The focus of this paper is IHC defined as a patient-centred, inter-disciplinary approach where there is a combination of conventional medicine with complementary and alternative medicine, with shared patient assessment, care or review and/or shared practice guidelines that are constructed and utilised during the care process. This therapeutic strategy enables each practitioner, often in conjunction with the patient, to contribute their knowledge and expertise towards providing individualized healthcare plans.”

In the second paragraph on p4 reference is made to ’adjunctive or complementary and not integrative’. These terms need further explanation. We also need to know why the authors think that it is important to distinguish between these approaches.

We have provided an explanation for the terms and the need to differentiate as follows:
“In this emerging field, there are no ‘right’ or ‘wrong’ way for patients to experience a combination of CM and allopathic medicine. Some conditions or people may be better suited to different processes of care. However, it is important to distinguish clearly between approaches which are adjunctive or complementary and not integrative as they are different entities, have different organisational and resource implications, and likely, different benefits. Adjunctive or complementary is where a therapy is used in addition to allopathic medicine but not involving any shared assessment, management or review in the process of care.”

In the third paragraph on p4, the authors refer to a ‘complex intervention’. The proposal that ‘many active components combine to provide outcomes that are greater than a sum of its individual parts’ needs further explanation. Alternatively, this sentence could be deleted.

We have more clearly defined by what is meant by ‘complex intervention’ as follows:

“IHC is a ‘complex intervention’ and hence, using experimental design with a complex intervention is challenging but feasible. By ‘complex intervention’ we mean that there are many active components, which may combine to provide outcomes greater than a sum of its individual parts; that may have involve complex systems or mechanisms for delivery; may be difficult to replicate (tailored to individual); and may be influenced by the environment and social context.

In the last paragraph on p4 the authors refer to ‘shared care’ and ‘shared context’. The difference between these terms needs to be made clear. Alternatively, the authors could choose the most appropriate term and use it consistently.

We agree and have removed references to ‘shared context’ and retained ‘shared care’ only.

Method

On p6, the second paragraph defines ‘process’ as ‘the way in which the health care is delivered - triage, referral, diagnosis, treatment plan and review.’ Where is the treatment or intervention in this? From the standard data extraction form, perhaps ‘intervention/duration of treatment’ should also be considered as part of the process of care.

We have included duration and types of treatments within the concept of ‘treatment plan’ and explained it in the amended Methods section. The ‘intervention’ is the therapeutic strategy of IHC:

“We were particularly interested in the process component of this model. We defined process as the way in which the healthcare is delivered – triage, diagnosis, treatment plan, and review. Central to this process are the means for collaboration to foster the “integrative” nature of the intervention. These concepts are explained below:

1. ‘Triage’ in this context refers to how a patient is ‘allocated’ into an IHC intervention or in a clinical context to a practitioner for initial assessment. In clinical practice the gatekeeper for this process may be the receptionist, the practice nurse, or general practitioner (GP) or may come from an external referral.
2. ‘Diagnosis’ refers to initial assessment where baseline data is collected in a clinical trial or where an integrative healthcare assessment is undertaken in clinical practice.
3. ‘Treatment plan’ refers to how the plan is derived, who is consulted, how it is agreed, types of treatments, duration, patient preferences and arriving at responsibility for the patient’s journey through the IHC process.
4. ‘Review’ refers to measuring outcomes at set time points, tracking patient compliance,
5. ‘Means for collaboration’: this may include meetings, shared charting, electronic medical records (EMR), corridor conversation, shared education and training, case conferences."

Results

Results other than those that focused on the authors' definition of 'process of care' are presented, again suggesting a review of the title and abstract to align more closely with the Methods and Results sections of the paper.

If intervention and duration of treatment are considered part of the process of care then the results will need to be reordered. In fact, the description of the study treatment plans in the third paragraph on p8 could be moved to the paragraph on 'Process of care: treatment plan' on p10. The authors may have good reasons for wanting to present the results in the current order but such reasons are not made clear.

We have undertaken a considerable reorganisation of the Results section:

*Process of care: Triage and Diagnosis*
*Process of care: treatment plan (which includes duration, types of therapies and Comparators)*
*Process of Care: Review*
*Process of care: means for integration and collaboration*

The last line of the first paragraph on p12 states, 'The risk of bias of the included trials is low if the difficulty of blinding is considered'. Please clarify this statement, perhaps with reference to Table 3.

We have clarified this statement and provided a reference to Table 3 as follows:

“The risk of bias of the included trials RCTs is low if the difficulty of blinding is considered (see Table 3). Blinding of participants and care providers in a trial where treatment is individualised is not possible. However, outcome assessment may have been blinded, one study achieved partial blinding of outcome assessment.

Discussion

The discussion section raises some important points but needs more cohesion. Paragraphs seem to jump from one point to point in a disconnected way.

We have undertaken a substantial rewrite of the Discussion section and hope that it now flows more cohesively.

Some statements need further clarification. For example, the last sentence in the second paragraph on p13, 'However, consideration could be given to the suitability ... ' needs more explanation. Why do the authors think that such consideration could be given?

Clarification has been provided as follows:

“To reduce resources, consideration could be given to the suitability of the information gathering stage being completed by a nurse practitioner, physician assistant or health coach or research staff as was done in two of the reviewed studies.”
And again at the end of the second paragraph on p15, the authors say that 'it would be extremely useful to know if IHC models are cost effective'. This sentence could continue with the reason(s) why the authors think this.

We have amended this paragraph as follows and hope this adequately provides clarification:

“From the reviewed studies, it is difficult to determine the type and level of resources required to conduct IHC patient assessment and treatment planning. Patient assessment and enrolment in the trials was typically undertaken by one or two therapists this may increase cost. Likewise means for collaboration such as meetings are costly. Any additional duties typically come at a direct financial cost to fee-for-service practitioners or need to be compensated for within the IHC model. Conversely it thought that within the integrative whole person approach there is considerable potential for cost-effectiveness [71]. Some preliminary data shows that various CM interventions may be cost effective [87]. It is important for the decision-making of consumers and policy makers to know if IHC models are cost effective. “

In the third paragraph on p14 the authors refer to 'whole system practitioners' (see note in Introduction above). Consistent use of terminology and clear definitions of the terms used in the paper will greatly enhance the reader’s understanding.

‘Whole system’ has been defined. The term ‘whole system practitioners’ has been removed.

Minor essential revisions

Abbreviations. Please check the use of abbreviations throughout. The first time a term is used it should be written in full, followed by the abbreviation in brackets. The abbreviation should be used in every occurrence after that. See in particular 'complementary medicine' and 'integrative health care'.

Thank you for noticing this. We have checked abbreviations and made amendments.

Health care occurs both as 'health care' and 'healthcare'. Either is appropriate but you need to be consistent.

We have made healthcare consistent throughout the document.

There are a number of sentences that are written in awkward English or require different punctuation. For example, in the last paragraph on p3, 'a variety of ways, a multi-disciplinary or inter-disciplinary way'.

We have amended the paragraph to read as follows:

“The team may operate in a multi-disciplinary or inter-disciplinary way. This may involve a democratic referral system or perhaps with the allopathic physician as the gatekeeper and the CM practitioner as adjunct practitioner.”

In the second paragraph in the discussion the referencing style for Murthy, Sibbritt et al, needs to be changed.

Referencing now formatted.
In the second paragraph on p16, the sentence 'These considerations aside, patients are already integrating ...' needs a reference.

We have provided a reference to this statement.

The terms 'conventional medicine', 'allopathic' and 'biomedicine' are all used. Could the authors use one term consistently or use clear definitions of the differences between the terms?

We have chosen to use the term “allopathic” and have used this consistently throughout the manuscript.

Avoid one sentence paragraphs. On p9, I suggest moving 'The feasibility ....' to the end of the paragraph above. Similarly on p10, I suggest moving the sentences beginning, 'The initial assessment ... ' and 'Only one study...' to the paragraphs immediately above.

We have tried to improve the expression in the manuscript including the removal of one sentence paragraphs.

On p13 last paragraph, replace 'consult' with 'consultation'.

Thank you this has now been amended.

Reviewer #2 Comments

Major Compulsory Revisions

The first issue, which I think is very important, is the development of the methodology employed within an integrative healthcare clinic and how that is developed. Clearly that needs to be transparent in the context of this complex intervention and not enough attention is paid to how this occurs and what general lessons we can draw from it.

Thank you and we agree. We have undertaken a substantial rewrite of the paper to address your comments. Specifically:

“To understand the IHC interventions – what works and what doesn’t – we need as much transparency as possible. The studies we reviewed were well supported by development plans or protocols documented. These documents provided a consistent structure, process and functional intent around the variable components of IHC intervention. The completed trials in the review provided several papers reporting the results of various aspects of the intervention. In the majority of the studies this was sufficient detailed to enable the replication of elements of the design, although a clear parallel evaluation of the process would be of benefit. Only one study in our review included a nested ‘process evaluation’[37]. Process evaluations within trials explore the implementation, receipt, and setting of an intervention and help in the interpretation of the outcome [58]. A process evaluation embedded within future trials may assist in documenting the time taken to construct a patient profile; the skills needed to collect the information for the patient profile; the time needed to devise a treatment plan, present the plan and reach consensus; help to distinguish between essential and non-essential components of the intervention; investigate contextual factors that affect an intervention; patient responsiveness; practitioner delivery; and monitor dose [24, 59, 60].


Equally as useful to understanding the IHC interventions is to know what ‘guides’ the treatment planning and management process beyond the integrative care and management. Table 4 includes a set of ‘guiding principles’ articulated by Maiers et al[61]. These principles serve to clearly delineate the intent or function of the intervention, and the approach the team should aim to take. Of these five principles, all studies were guided by Principles 4, 5 and 6. It was less clear the extent to which studies were guided by the other three principles.

The basic approach to the provision of care in each of the studies was guided by Principle 4: using evidence informed interventions and translate existing complementary and integrative therapies (CIT) into clinical practice bringing together practitioner expertise, patient presentation and preference to form the treatment plan [62]. In some studies, the organisational process of constructing a treatment plan was documented and this is useful for future replication. Some of the trials then documented the frequency and types of treatments patients received although the details and rationale of the actual treatments are not provided. Journal article length make this level of reporting unfeasible, . Understanding frequency and intensity of the individualised treatments may be graphically depicted in ways suggested by Perera [63]. This may provide an indication of ‘dose’ per individual. The use of an inadequate dose may be safe and less resource intensive but ineffective.”

The authors suggest a process definition of triage, referral, diagnosis, treatment plan and review; that’s very valuable and better definitions of these areas would be enormously helpful for future researchers.

Thank you for your comments. We have been defined these concepts more fully in the Methods section as follows:

“To explore the structure and design of the IHC intervention we applied the structure-process-outcome model [30]. The structure being defined as the environment in which healthcare is provided, the process as the method by which healthcare is delivered and outcome as the consequence of the healthcare provided. We were particularly interested in the process component of this model. We defined process as the way in which the healthcare is delivered – triage, diagnosis, treatment plan, and review. Central to this process are the means for collaboration to foster the “integrative” nature of the intervention. These concepts are explained below:

1. ‘Triage’ in this context refers to how a patient is ‘allocated’ into an IHC intervention or in a clinical context to a practitioner for initial assessment. In clinical practice the gatekeeper for this process may be the receptionist, the practice nurse, or general practitioner (GP) or may come from an external referral.
2. ‘Diagnosis’ refers to initial assessment where baseline data is collected in a clinical trial or where an IHC assessment is undertaken in clinical practice.
3. ‘Treatment plan’ refers to how the plan is derived, who is consulted, how it is agreed, types of treatments, duration, patient preferences and arriving at responsibility for the patient’s journey through the IHC process.
4. ‘Review’ refers to measuring outcomes at set time points, tracking patient compliance,
5. ‘Means for collaboration’: this may include meetings, shared charting, electronic medical records (EMR), corridor conversation, shared education and training, case conferences.”

The authors suggest there’s some evidence for effectiveness for individualised integrative healthcare packages versus control treatments. The strengths and limitations of control versus integrative
healthcare packages are not discussed; are we dealing with an enhanced non-specific effect associated with increased health literacy and educational input? It’s an important question to address methodologically.

Obviously there will be a debate about specific versus non-specific outcomes versus quality of life outcomes in association with health economics, clearly the need for long-term follow-up as in the majority of instances integrative health is utilised in chronic long-term conditions. These need not be debated at length as many of these points will be made elsewhere.

We have more fully discussed the strengths and limitations of IHC packages vs control and attempted to address the issues raised above in the following:

“Measuring outcomes and designing IHC interventions is further complicated by understanding that causality lies for the effectiveness of an IHC intervention lies not just with the treatment component but by enhancing the healing capacity of the patient (salutogenesis) through the social context and healing environment [72]. The patient focused, IHC team based approach is thought to enhance this process as team members contribute unique perspectives, skills and experience to patient care [73, 74]. Bell argues that the whole therapeutic strategy of IHC needs to be evaluated: including the patient-provider relationship, multiple conventional and CAM treatments, and the philosophical context of care as the intervention. Only one of the studies in our review included measures to attempt to evaluate this process [75]. Future clinical trials of IHC interventions should include qualitative elements that seek to understand the ways in which this process may be fostered to maximise the specific and nonspecific healing effect of an IHC intervention.

The strengths of an IHC intervention to provide good external validity need to be considered against the inherent limitations of undertaking the evaluation of a complex intervention using an experimental design (see Table 5). Defining and articulating the “black box” of an IHC intervention is important for internal validity, generalizability and replicability [58]. The difficulty in doing so within this type of trial design is one of the key limitations of a complex intervention. The individualised nature of IHC makes it difficult to know which component of the intervention is exerting the main effect - the combination of the therapies, the extra attention or the patient-practitioner relationship.

Table 5: Strengths and Weakness of IHC intervention studies

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Challenges/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individualised, tailored</td>
<td>Active components are obscured</td>
</tr>
<tr>
<td>Aims to heal the whole person</td>
<td>Difficult to replicate</td>
</tr>
<tr>
<td>Suits chronic conditions</td>
<td>Poor internal validity</td>
</tr>
<tr>
<td>Good external validity</td>
<td>Not readily transferrable to other sites as dependent on availability of modalities,</td>
</tr>
<tr>
<td></td>
<td>certification of providers, cost</td>
</tr>
<tr>
<td>Potential to reduce health costs</td>
<td>May require a long trial period with follow up to establish efficacy and cost</td>
</tr>
<tr>
<td></td>
<td>effectiveness</td>
</tr>
<tr>
<td>Non-specific benefits due to increased attention, health literacy and education.</td>
<td>Non-specific benefits may be practitioner dependent.</td>
</tr>
</tbody>
</table>
I think the authors need to think very carefully about the messages they want to put across about:

- The design of integrative healthcare setups.
- The study models that should and could be proposed along with the relevance and need for appropriate controls. The authors may consider issues such as Zelen designs within this context.
- A simple list of appropriate outcomes and considered duration of care.
- The kind of conditions in which they genuinely see integrative healthcare may be applied in a Western context.
- A preliminary assessment of the strengths and weaknesses of the current research with a much clearer strategic approach in terms of the way forward (perhaps diagrams and tables may help in this context).

The authors do clearly acknowledge the work on which this is built, the title and abstract do convey the substance of the article but I believe the conclusions of the abstract could be more strategic and methodological. The writing style is good and has real clarity.

This article would benefit from slightly more clarity in relation to the research question and considerably more clarity in relation to the discussion.

Thank you for these very useful comments. We have attempted to address the above issues throughout the paper but specifically in the following.

“For the purposes of research, IHC is a therapeutic strategy not a single drug intervention. Team-based, patient-centred, integrative approaches to care present a challenge to designing rigorous studies, given IHC is typically used to provide many simultaneous treatments for multiple health concerns [67]. Many efforts have been made to propose frameworks for researching complex healthcare such as IHC [29, 58, 59, 68] calling on program theory [73], whole system theory [68, 72], utilising the Medical Research Council (MRC) framework or employing implementation, process or fidelity evaluation[58]. Research methodology for evaluating IHC probably best involves a combination of understanding the philosophical underpinnings of IHC through whole system theory and examining it within the MRC framework. Whole systems can be defined as “approaches to healthcare in which practitioners apply bodies of knowledge and associated practices in order to maximize the patients’ capacity to achieve mental and physical balance and restore their own health, using individualised, non-reductionist approaches to diagnosis and treatment”[76]. In the case of IHC, it is the individualised integrative therapeutic strategy that is the whole system intervention.

The MRC framework follows a typical drug development pathway but provides guidance for identifying confounders, modelling to predict how components may interact and identifying the constant and variable components of the intervention. Within the MRC framework a nested “process evaluation” within the study would provide insight on the constant and variable components of the intervention. A process evaluation would investigate contextual factors such as setting, team composition and facilitation, and examine patient-provider expectations and relationships [24]. A process evaluation may follow some of the dimensions identified in program implementation theory: fidelity, quality of delivery, participant responsiveness, and program adaptation [77]. Each of these dimensions has been demonstrated to influence outcomes. Strategies may include interviews, focus groups, and observations alongside document reviews of
Clinical files and correspondence. An additional complexity is that, not unlike conventional interventions for chronic and complex conditions, research needs to be conducted over the longer term to truly capture outcomes. Jonas et al document an evaluation model for integrative care specifically for cancer but equally applicable to understanding and evaluating IHC in primary care [72]. The model is designed to collect data on wellbeing, behavior, clinical outcomes, bio-measures, costs and the course of treatment and compare IHC with standard healthcare practices.

A further challenge in IHC research is the preference of researchers and funders typically prefer investigations that are linear, showing a clear cause and effect, with few confounders and cost effectiveness can clearly be determined (Nisbett 2003, [4]. Complex “systems” with multiple levels of relationships and multiple factors are interactive and iterative and do not fit into this preferred type of research (Nisbett, 2003). The typical efficacy focused RCT prescribes to the ‘average’ patient and is ‘fundamentally’ at odds with CM orientation to the ‘individual’ patient (IOM, 2005). The number of patients using CM continues to grow, as does the number of patients that desire a general practitioner who communicates about, and refers to, CM practitioners as necessary. Patients are seeking care that is tailored to their individual needs and where CM and conventional medicine collaborate [78-81] with availability of these treatment options in one location being cited as desirable [78]. These considerations aside, patients are already integrating conventional and CM therapies on their own due to a desire to access the best that both healthcare paradigms have to offer[82]. Investigations on the efficacy, safety and cost effectiveness of an IHC model of care are warranted to guide health policy makers and consumers in decision-making and there are sufficient research and statistical methods available that enable such investigation.

Proposed RCT designs for complex interventions include pragmatic trials, factorial design, preference trials and randomised consent designs, N-of-1 designs [Verhoef, Lewith 2005]. These trial designs may be used to address the preferences of patients, which are often strong in CM users, for an integrative approach [83]. In considering comparators and research design, there is a broad consensus that the evaluation of IHC and CM be conducted where possible within a comparative effectiveness framework [29, 84, 85]. The Institute of Medicine defines CER as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care [86]. In selecting comparators for an experimental design, IHC lends itself with some ease to comparative effectiveness studies. “

We thank the reviewers for their thoughtful comments and believe the manuscript is stronger as a result of their feedback. We hope these amendments are satisfactory and we look forward to learning the outcome of this manuscript.

Yours Sincerely,

Dr. Suzanne Grant