Author’s response to reviews

Title: MAGnesium sulphate for fetal neuroprotection to prevent Cerebral Palsy (MAG-CP) - Implementation of a national guideline in Canada

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Version: 1 Date: 12 Oct 2017

Author’s response to reviews:

Response to reviewers’ comments, Implementation Sci 2017

We appreciate the feedback on our paper, "MAGnesium Sulphate for fetal neuroprotection to prevent Cerebral Palsy (MAG-CP) – a managed knowledge translation project to implement guidelines in Canada". Below, please find responses to the reviewers’ comments, in bolded italics.

Referee 1

This paper describes and evaluates results of a managed Knowledge Translation (KT) intervention (MAG-CP) funded by the Canadian Institutes of Health Research and aimed to increase optimal use (i.e., administration when and only when indicated) of MgSO4 for women at risk of imminent birth to reduce the likelihood of cerebral palsy in the child. The proposed multifaceted KT intervention included national clinical practice guidelines, education (a national online e-learning module and at project's sites, educational rounds), engagement of health care professionals (focus group discussions, site visits, etc.), and identification of barriers and facilitators (survey). In order to evaluate the effect of the KT intervention two databases have
been used: (i) the Canadian Perinatal Network (CPN) database, (ii) the Canadian Neonatal Network (CNN) database.

We agree with this summary, although in response to comments received and for clarity, we have removed the term ‘managed KT’ from the title and from the text.

An interrupted time-series analysis was used on data provided by CPN participating sites to track the use of MgSO4 for fetal neuroprotection (NP) prior and during the KT intervention and evaluate the optimal MgSO4 use. CNN data have also been used in order to expand the analysis to sites not included in the MAG-CP project and examine the impact of MgSO4 for fetal NP on delivery room intensive neonatal resuscitation (an outcome not available in the CPN).

The paper outlines approaches and results of great interest, which are very promising for future applications in the implementation of evidence-based practices into clinical and organizational local contexts. Hence, this work fits well with the Implementation Science's fields of interests and I recommend the acceptance of the paper after major revisions.

The contribution of this work to research and practice is twofold:

(i) It represents the first multicentre KT initiative to report results and is based on a large dataset (data represent 78% Canadian tertiary perinatal centres over a period of 11 years)

(ii) It proposes a multifaceted KT strategy, which has shown to be effective to increase the optimal use of MgSO4.

Rather than focus on the obvious strengths of the manuscript, which make this research a valuable work to be spread within the scientific community, I also have some comments that I describe below. I really hope that these comments will be helpful to revise the paper.

A. A general comment is that the contribution of this work in terms of proposed KT strategy should be better valued and contextualized in the existing literature.

We designed the project to focus on guideline implementation, and it was the first project in Canada in which national guidelines had been actively implemented. In response to feedback, we have revised our introduction extensively. We have provided more detail about the pre-MAG-CP gap in practice of using magnesium sulphate for fetal neuroprotection in the setting of imminent very preterm birth (page 5, line 78). Also, we have provided better rationale for the use of a multifaceted KT strategy, and expanded our discussion to include our previously published findings about the relative merits of our various strategies (page 6, line 91).
We have also added to our future directions that in terms of future directions, ascertaining which component of the multifaceted strategy works for other health interventions are needed (p 25, line 495).

B. I would suggest clarifying the gap which this work aims to fill and objectives of the paper in the "introduction" - e.g. (i) describe a multifaceted KT strategy (…), (ii) assess the effectiveness of the strategy (…).

Thank you, we have added this to the objectives (p. 6, line 104).

C. In order to help the reader to go throughout the paper I would suggest adding a reminder of the sections of the paper at the end of the "introduction".

Thank you, we have added this sentence to the end of the introduction: “This will be done by describing our KT strategy and targeted sites, outcomes, and data analysis using data from the Canadian Perinatal Network (CPN) and Canadian Neonatal Network (CNN). (p. 7, line 111)

D. In the "introduction" (or as a subheading) a literature background on KT strategies / audit and feedback should be added. This would help to support the approach proposed and to identify and discuss strengths of this approach (which is shown to be successful in this context) compared to other approaches. I am aware that some literature and some reflection on this have been introduced in the "discussion" (line 343 - 352), but I think it is important having an introduction on KT strategies before presenting the proposed KT approach and then discuss the strengths of the proposed approach compared to previous studies. This would improve the perceived value of the work.

Below some literature on audit and feedback:


Thank you, we have added more context to the Introduction under the subheading “KT Strategies” and used three of these four references (p. 6, line 91). We did not use the reference by Foy et al., due to the heterogeneity of the studies included in the review, and its generalisability.

E. Paragraphs "CPN data collection - in the pre-MAG-CP and MAG-CP eras" and "Canadian Neonatal Network (CNN) data collection" describe not only data collection but also data analysis methods - maybe it could be helpful rename them (add "analysis" or remove "data collection")? The same in the results (the term "data collection" in the titles might be confusing).

Thank you, we have made this change and added “analysis” to the heading title, and removed “data collection” from the heading in the Results section.

F. It would be better broke in two or three sentences the sentence line 138-143.

Thank you. We have broken this down (line 207-212).

G. It would be better number, use bullet points or put in a table the sentence line 167-178

We have placed this into the text as these are already placed in the Results section in Table S7 of the appendix. Being mindful of reviewer #2 who requested more judicious use of tables, we have not added an extra table; however, we have revised the text to simplify the description of our ranking of engagement in hopes that this would be sufficient, whist also adding reference to Table S7 that provides additional detail that we have now deleted from the text. We would be happy to add an additional main table if the editor so wishes.

H. Finally I would also suggest expanding the discussion.

Thank you. We have done this (line 407 onward).
Referee 2

Many thanks for the opportunity to review this interesting manuscript. Following are suggestions to clarify essential details about the objectives, and intervention design and evaluation so that it is more apparent to readers what was done, how they can apply the findings, and the contribution of this work to the field of implementation science.

INTRO

* The reporting of weeks of gestation (i.e. value with a superscript number) will not be understood by non-experts - is there another way to report this?

Thank you for pointing this out. We have converted the format to weeks and days to improve clarity throughout the text, tables and figures.

* Line 68-69 provide some statistics to be explicit about safety and effectiveness as deduced by meta-analyses

We have included information about our sample size calculations (p 11, line 185), briefly here but in more detail in the methods of the paper. No adequate estimates were available for neonatal resuscitation.

* Include references and/or elaborate on details for assertions, i.e. sentence ending line 72 (controversies), line 74 (not routinely delivered) and line 75-76 (how is 'managed knowledge translation' defined?)

We have now included references for these assertions (line 72-77), and have changed ‘managed knowledge translation’ to simply a knowledge translation intervention.

* Line 78 - instead of referring to 'optimal' use just specify what is recommended

Thank you, we have better defined ‘optimal’ use (line 106), which is MgSO4 use to women delivering at under 32 weeks as indicated, and no use when not indicated. We have retained use of the term ‘optimal’ for brevity.
* Line 79 - why is 80% the target or benchmark? Elaborate and provide a reference

We chose 80% as the standard benchmark for an intervention with a grade 1A recommendation in clinical practice guidelines. We have now added this rationale to the manuscript (line 107).

* Line 80 - exploring adverse effects leads the reader to believe that the purpose of this research is to evaluate a clinical intervention (to establish safety) rather than a behavioural intervention - presumably clinical effectiveness and safety would have been established before investing resources in KT to disseminate/implement knowledge and promote use of MgSO4 - therefore the objectives are confusing* consider reporting safety data in a separate manuscript

In our initial discussions with centres as part of the implementation process, maternal safety was a concern, as it is for the usual indication of maternal eclampsia/pre-eclampsia. Clinicians wanted to ensure that the safety profile of magnesium sulphate for fetal NP would be the same in real-world clinical practice as it was in the more controlled setting of a randomised trial. In the end, we saw few adverse maternal effects and certainly an insufficient number to warrant a separate manuscript. We have clarified that these safety concerns were a secondary objective.

To be clear, the outcome of infant ‘death or CP’ will be reported separately, given the substantial additional information that will need to be described, both in terms of methods and also results/discussion.

* Overall, the Intro is very brief; it would be useful to include evidence from Canada and elsewhere demonstrating that MgSO4 is not used, what is known about determinants or barriers/facilitators of use, etc. since these details are essential to informing the design of any KT intervention

Thank you, we have added further evidence that MgSO4 was not used previously, that it is used with variable frequency internationally, and that barriers include knowledge and fears about maternal safety (lines 82-90).

**METHODS**

* Any manuscript describing a behavioural intervention should mention and reference reporting standards that were employed such as WIDER, StaRI, TIDieR or SQUIRE (for quality improvement)

Thank you, we have added that this manuscript followed the StaRI guidelines (line 120).
* Any manuscript describing the development and evaluation of a KT intervention should describe and reference the theory or theoretical rational upon which the intervention was based (see WIDER) or Nilsen Implement Sci 2015 on implementation theories, models and frameworks.

As per comments of Reviewer #1 on proposed approach and Reviewer #3, we have added to the introduction the Theory of Diffusion on which our KT intervention was based upon in the Introduction (line 91).

* Justify use of research design employed

Thank you, as per Reviewer #3, we have clarified in the methods why an interrupted time-series study design was used (i.e., a powerful quasi-randomized design that allows us to examine the effect of the intervention distinct from effects that may occur unrelated to the intervention) (p 13, line 239). Further emphasis has been added in the discussion related to a strength of the paper (line 457).

* Justify use of a multifaceted intervention since Squires Implement Sci 2014 meta-analysis showed that single interventions can have similar impact to multi-faceted interventions

Thank you. MAG-CP was started prior to the published evidence cited. Nevertheless, according to the review cited, we understand that in general, multifaceted interventions are not necessarily better than single interventions, nor are they inferior. Also, further editorials and commentaries have stated that in specific circumstances, other factors (such as the complexity of the health intervention or the organizational culture/characteristics [Rogers 2003]) can influence effectiveness. We examined our data with the goal of identifying which aspect of the intervention may have been most beneficial; however, we found that no specific element that was superior to others [Teela et al. 2015].

* Justify why an educational intervention was employed given that systematic reviews show that educational strategies have a small impact on behaviour; it is insufficient to say that benefits/challenges of the interventions were published previously - this manuscript should be self-contained and provide the reader with enough information to understand the rationale and design of the intervention employed.
As stated above and revised in our introduction, we identified knowledge gaps as barriers to implementation of MgSO4 for fetal neuroprotection; as such, it was important to include an educational component as a component (but not the only component) in our strategy. Our education component was not passive, an approach that may not be effective when used alone. Rather, we employed active educational interventions, such as the site visit and e-learning module for active self-study, in conjunction with our other interventions [Wensing et al. 2010]. We have now clarified and justified this in our introduction (line 101).

* Line 89 "The KT consisted of…” would be more appropriately referred to as "The intervention consisted of…”

Thank you, we have made this change (line 122).

* Provide the reader with details about AdvancingIn and clarify any conflicts of interest - are the members of the research team the executives?

Advancing In is an online continuing medical education platform for clinicians and health professionals, and we have clarified this in the manuscript. The module was developed by the senior authors of the guideline on behalf of SOGC, who separately contracted AdvancingIn to provide a platform for this project, as an in-kind contribution. Neither our guideline committee not our study team had a financial or any ongoing relationships with AdvancingIn.

* Provide more details about sampling and recruitment, and a calculation or estimate of how many participants were needed

We have added a description of the sample size calculation to the methods, as follows (line 185):

Sample size calculation

Over the four years of the KT strategy, we anticipated recruitment of 3752 mothers based on previous CPN enrollment of women at <29 weeks (from the CPN inception in 2005). We estimated that we would have >95% power (two-sided alpha of 0.05, <10% baseline use of MgSO4 for fetal NP) for each of two scenarios: (i) ‘planned’ rates of MgSO4 use for fetal NP of 20, 40, 60, and 80% by the end of years 1-4, respectively, and (ii) ‘pessimistic’ rates of 20, 30, 40, and 50% by the end of years 1-4, respectively, based on a prior survey with the centres. The power calculations were made without adjustment for random effects (i.e., clustering), because the calculations for these adjustments also require specification of the distribution of MgSO4 use across hospitals in the four-year study period, and these were not known.
For adverse maternal outcomes, we estimated at least 80% power to detect potential increases in serious maternal adverse effects reported in RCTs: hypotension (RR 1.51 [1.09, 2.09] from baseline of 6.5%), infusion stopped due to adverse effects (RR 2.81 [2.01, 3.93] from 2.6%), respiratory depression (RR 1.31 [0.83, 2.07] from 1.9%), and pulmonary edema (RR 2.79 [0.74, 10.47] from 0.3%).

No increase or decrease in stillbirth or neonatal death was anticipated, but we were powered to detect only substantial increases in these outcomes (i.e., an increase of 27-28% in total paediatric mortality under the planned and ‘pessimistic’ pre-specified rates of MgSO4 use).

* Line 120 - provide more detail about how sites tracked their KT activity - what does this mean?

We have clarified this in the manuscript (line 161). We asked sites to record answers to a number of types of KT strategy employed locally, using a web-form; this included number of times that the local team participated in teleconferences, and other local activities, such as presentations, reminders, or informal conversations and ‘teaching moments’.

* Line 167 - define or specify criteria used to distinguish highly or less engaged and the process that was used to confer these designations

The criteria used to distinguish engagement was based on items found in Table S7 in the appendix (and also summarized in line 161-170). ‘Highly engaged’ sites had values at or above the median or mean for each activity assessed. The assessment was done independently by each member of the Working Group, with agreement reached by consensus.

* The Methods are somewhat confusing because there were multiple components and it is not readily clear how they were linked or complementary, or what is meant by pre and post or eras or epochs - consider using more sub-titles in the Methods for essential elements such as sampling and recruitment, data collection, data analysis, etc.

Thank you. In the methods section, we have added sub-headings and better clarified the pre- and post-MAG-CP eras - the pre-MAG-CP era (before the intervention) and MAG-CP era (during the intervention). The pre-MAG-CP era was sub-divided into three time periods, and the MAG-CP era was divided into nine six-month time periods; we have now better clarified the rationale for this.
RESULTS

* Use sub-titles to separate the reporting of data for different study components or impacts/outcomes that were assessed

Thank you. We have added this.

* An alternative option is to split the findings across more than one manuscript, which may also help to simplify/clarify the Methods

Thank you for this suggestion. As stated earlier in response to your comments, the information on maternal safety was identified by us as a barrier to implementation, just as it is for MgSO4 for eclampsia treatment and prevention. As such, we felt that it was important to try to include this information in the manuscript; as it happened, this was manageable as there were few maternal side effects observed and there would not be enough information for a separate manuscript.

* Consider more judicious use of in-manuscript and online-only tables/files

Thank you. We have tried to include only key tables and figures in the manuscript, but included the others as online-only/appendix files for transparency. We are happy to consider specific recommendations.

DISCUSSION

* To what is the "significant increase" attributed given that the intervention was comprised of multiple components?

There was not enough power to specifically detect which component of the intervention was more influential in changing clinical practice. We have stated this in our limitations. What we can confirm is that each of the component of the intervention revealed different types of information [Teela et al. 2015]. Depending on the intervention in the future, clinicians can look at our experience and choose which components are best-suited to aid implementation.

* Line 344 - the Straus article published in 2013 may state that multifaceted interventions are more effective than single interventions but the most recent and robust evidence (Squires 2014) disagrees

Please see above comment under ‘methods’.
Many of the references cited are quite old, i.e. line 352 reference #35 is 1995; discuss the findings of this study in relation to more current evidence.

Thank you, we have updated our references, particularly as directed by the reviewers, for issues such as implementation frameworks (Nilsen P. Implementation Science 2015), justification of KT strategies, and justification of multifaceted strategies (refs 21-25).

Line 362 - this is certainly not the first study to report a multicentre KT initiative - do the authors mean in relation to MgSO4 use?

Thank you. Yes, we did mean implementation of both MgSO4 for fetal neuroprotection and of national SOGC clinical practice guidelines. We have provided this clarification in the manuscript (now line 450).

In the discussion of limitations add that theory or pre-established barriers were not used to select and tailor intervention design, and there was no evaluation of implementation fidelity, and no qualitative component to more thoroughly assess why/how the intervention worked; also discuss the generalizability/transferability of the findings.

Our intervention was designed as a central package, consisting of the guideline, e-learning module, and initial tools (pre-printed orders).

We did use theory (Theory of Diffusion) and some pre-established barriers to tailor our intervention design (e.g., pre-printed orders to raise confidence of staff in prescribing MgSO4 safely). Also, we responded to additional barriers identified in our surveys and site visits, by developing other tools for professionals, such as decision-aids, a summary of the literature regarding the effect of the intervention on fetal heart rate and pattern [Nensi et al, 2014], and a summary of protocol standardization [De Silva et al, 2015].

Efforts were informed by qualitative analysis early in the project. We have previously published a detailed qualitative analysis of three of our KT strategies in the first year of MAG-CP [Teela et al. 2015], and we have added more information from this analysis to the manuscript. We have added a statement on generalizability of the findings: “As such, we believe our KT findings are generalizable to other clinicians who administer MgSO4 and manage threatened very preterm birth, decision makers, and researchers wishing to implement a health intervention or change practice.” (line 464)
In addition, we did examine fidelity, although we have now made this clearer. Please also see our comment to Reviewer #3 below.

* Comment on the overall contribution to the field of implementation science

We have demonstrated that we can move from evidence-based national policy to implementation through a model of central support for local teams, an approach that should be feasible for other interventions. We have added this to the conclusion (line 487).

* Include a section for ongoing research that is warranted given these findings

Thank you, we have added this to our manuscript: “In general, future work should explore which components of a multifaceted strategy are particularly useful for implementing certain types of health interventions, such as drug interventions or surgical manoeuvres.” (line 495)

Referee 3

This paper describes an implementation study designed to increase optimal use of MgSO4 for fetal NP to 80% in eligible women admitted to participating tertiary centres in very preterm labour. The authors described 4 KT strategies used: (1) the Society of Obstetricians and Gynaecologists of Canada (SOGC) clinical practice guideline on the topic that was published in May 2011; (2) an e-learning module; (3) a 'Barriers and Facilitators Survey'; and (4) site visits and other interactive activities between the central MAG-CP team and individual sites (e.g. monthly newsletter, teleconferences, supportive emails and one-on-one support for questions and advice, provision of KT tools such as pre-printed physician orders, presentation materials, information sheets for staff and women and reminders for women who were being expectantly managed in hospital and at risk of preterm birth at <32 weeks). A robust interrupted time series analysis was completed to measure the effect of the KT strategies to improve use of MgSO4 for fetal NP.

Abstract - Required revisions:

* The abstract includes a clear statement supporting the need for MgSO4 for women at risk of very preterm birth to reduce the likelihood of cerebral palsy in the child, a brief description of the study design, methods, KT strategies used, the primary outcome, key results and conclusions of this project.
Recommendations: (a). Include a statement describing the extent of the practice gap (e.g. baseline practice rates compared to optimal),

Thank you. We have included baseline practice rates in the introduction, as well an estimate in the abstract. (line 83)

(b). Explicitly identify this as an implementation study - current wording used is 'managed KT intervention' which is not clear and needs to be defined in the body of the paper if used, and

The title has been changed to emphasize that this is an implementation project. As per Reviewer #1, we have changed ‘managed KT’ to ‘multifaceted KT’ for clarity.

c) Describe secondary outcomes of interest as well.

We have clarified that our secondary outcomes of interest were related to safety: maternal effects and effect on neonatal resuscitation.

Background and supporting literature - Required revisions:

* The authors provided rationale and supporting literature for use of MgSO4 for women at risk of very preterm birth to reduce the likelihood of cerebral palsy in the child.

* They described issues that were perceived to be barriers to uptake of this practice (e.g. concerns about potential effect of MgSO4 on FHR and increased neonatal resuscitation, lack of understanding of neuroprotective mechanism of action and inadequate studies describing long-term adverse pediatric outcomes other than CP).

* The purpose of the study is clearly stated: "increase 'optimal' use of MgSO4 (i.e., MgSO4 use when and only when indicated) to 80% of eligible women over four years (2011-15), as well as document any maternal or fetal adverse effects".

Recommendations:

a. Line 75-76 - 'managed knowledge translation (KT)' should be defined.

This phrase has been replaced by ‘a knowledge translation intervention’ for clarity.
b. It would strengthen the manuscript to include data to demonstrate the pre-study variability in use of MgSO4 for fetal NP and provide evidence of the practice gap (e.g. baseline rates, practice variation across sites or regions) to justify the need for this study.

Thank you. We have added a study that we conducted and published in 2015 on baseline rates. We scoped out existing knowledge resources and use of MgSO4 for fetal neuroprotection; however, there were few guidelines and no implementation studies at the time. Despite the trials and meta-analysis, we found that in 2010 and 2011, only 1.5% of women with threatened preterm birth before 32 weeks received across Canada. We have added, “A previous study on existing knowledge resources about MgSO4 for fetal neuroprotection in Canada found that despite the convincing evidence of effectiveness, use of MgSO4 for fetal NP was near non-existent (1.5%) between 2010-11, and there was no such use of MgSO4 before 2010.” (line 82)

c. Clarify terminology - Need to differentiate between the healthcare intervention being implemented in this study (e.g. use of MgSO4 for fetal NP) and the multi-faceted bundle of implementation strategies that were used to implement the intervention (e.g. guideline, e-learning module, audit and feedback, barriers and facilitators survey and 'other activities' etc.). The terminology used throughout the body of the paper is inconsistent.

Thank you, we have better clarified the terminology throughout the manuscript.

d. Provide rationale for the implementation strategies selected and how these are expected to achieve effect. Other than listing the strategies on page 6 and providing a statement that "The benefits and challenges of these types of interventions have been published.[13]" there is no information provided justifying why this particular bundle of interventions was selected to address this particular practice issue within these practice settings. The theoretical framework(s) used to guide this study and inform the design of the KT strategies used should be described.

Thank you. We have included that the study and design of KT strategies were informed by concepts of Roger’s Innovation-Diffusion theory in the Introduction (line 92), and the exploration of barriers and facilitators were based on the Theoretical Domains Framework, in the Methods (line 142).

Methods - Required revisions The authors discussed and provided rationale for the ITS analysis and described the data sources used for the ITS. The authors also provided general descriptions of the 4 KT strategies used in this implementation study. No information was provided about the development or pilot testing of the 'barriers and facilitators survey' nor how the survey data was used to guide interactions with the participating sites.
Recommendations:

a. Page 6, line 87-88 - revise wording to say - "We used an ITS design to evaluate the effectiveness of a selected bundle of KT strategies to optimize use of MgSO4 for fetal NP"

Thank you, we have made this change. (now line 118)

b. To facilitate replication of the methods used in this study by other researchers: Provide background information about the development and pilot testing of the 'barriers and facilitators' survey - include a copy of the survey as supplementary information. What type of questions - pick list choices or free text? Who completed the survey for each site? Were there multiple respondents for each site - if so how did you handle their data as compared to a site with one respondent? How was the data analyzed? Expect to see some information in the discussion re: limitations of survey data - selection bias, and social desirability bias. How was the data from the 'barriers and facilitators' survey used as part of the implementation process?

Being mindful of Reviewer #2’s comment on judicious use of online information, we have not included a copy. We have included a reference to our previous publication on our comparison and challenges of KT strategies that we used, where the survey can be found. We have also included the types of questions included and the nature of respondents: The ‘Barriers and Facilitators (B&F) Survey’, informed by the Theoretical Domains Framework [Cane et al 2012], was distributed at each MAG-CP study participating site, by each site’s local team to be completed by at least five obstetricians and five nurses (to explore local barriers to and facilitators of MAG-CP implementation). The surveys were anonymized and consisted of mixed free text and tick choices, collected locally, and sent to the central team for compilation and interpretation to provide feedback of results to each site for their review. This approach was chosen to determine organization readiness and address challenges as well as identify knowledge gaps. Further details and copy of survey has been published in our detailed qualitative analysis [Teela et al, 2015]. (line 142-150)

c. Figure 1 - provides a schematic of the MAG-CP knowledge translation audit cycle - "monitoring use of MgSO4" and "provide feedback to users" were two components within this cycle - but this audit and feedback process is not listed as one of the distinct KT strategies used in this study (page 6). Given the fact that audit and feedback is a recognized evidenced based KT implementation strategy (supported by a number of Cochrane reviews) I think it has to be included as a discrete strategy in this study and should be described as such and referenced accordingly.
Thank you. We have made this change and clarified this in the manuscript (line 125).

d. Page 9 lines 167-182 - describes the tracking mechanism used by the researchers to monitor the extent to which the sites participated in the various KT activities. This data has been transformed into an 'engagement' measure. Expected to also see some reference to fidelity measures used to verify that the implementation strategies were delivered as intended. This is an essential component of any implementation study and different from the self-reported use of or access to KT resources.

We have clarified our methods regarding implementation fidelity, which we took to be those aspects of the intervention that were directly measured by us (i.e., e-learning module used, site visit occurred in order to disseminate SOGC guideline, Barriers and Facilitators Survey performed locally, and teleconferences attended as a reflection of interaction with central team that could provide feedback and suggest improvement based on data provided in the six-monthly audit and feedback cycles), along with other measures of potential moderators, such as participant responsiveness (e.g., use of pre-printed physician orders for MgSO4 prescription). These details have been added to the methods and results. (line 161-166, 286).

Results and Discussion - Required revisions:

* Discussion section - The results of the ITS analysis were presented in detail. *

Recommendations:

a. Because there is no justification of the KT strategies used, and no confirmation that the strategies were implemented as intended across all sites - it is difficult to determine whether the change in practice reported was due to the full 'KT bundle' or to specific components of the bundle (e.g. audit and feedback and face-to-face interactions during site visits) or simply due to increased awareness of and perception that 'someone was watching'. The question remains - were all of the implementation strategies built into this study essential to achieving the positive outcomes. This is an important question that has implications for future spread of this intervention and for sustainability of practice change long term. The implementation strategies used do have an associated cost (both in dollars and human resources needed to support the change) so it is important evaluate not only whether change happens, but to also understand why and how it happens and what resources were needed to support the change. At the very least this issue needs to be addressed as a limitation of the study. Spread and sustainability are important factors to consider as well and the authors are encouraged to address these issues in relation to implications for practice, policy change and future research.
We have provided more context and justification for our KT strategies used. We agree that we were unable to ascertain which components of the bundle were effective. We have previously published a comparison of strategies employed in the first year of MAG-Cp: e-learning module, barriers & facilitators survey, and site visit reports (audit & feedback). We found that all three were important in obtaining information and none was superior to the others. For example, site visits were important to obtain organizational-level barriers, while the surveys showed more information about social-level barriers, perhaps due to the anonymity provided compared to a face-to-face site visit.

We do not believe that awareness increased simply because we were monitoring MgSO4 use. All sites were part of the Canadian Perinatal Network that had begun data collection in 2005. Also, there remained substantial variability in use of MgSO4 across sites despite standardized data collection.

We agree that spread and sustainability are important factors. With regards to spread, we accessed the majority of perinatal centres across Canada where high-risk women eligible for the health intervention would be seen. These centres also provide regional support to hospitals where women might present in an unanticipated fashion.

This project was pragmatic and based on a sustainable approach: when a guideline is published, it can be undertaken by local teams provided that there is central support. The extra resources consumed in our project were a result of the need to collect data about usage of the health intervention. If health care systems were to routinely collect relevant information related to process and outcomes, the cost of the study would consist of creation of resources and support of local KT teams to move it forward through audit and feedback.

We have added a comment on costs and resources to our discussion section (line 426).

b. Page 17 - lines 342-350 - acknowledges the evidence that indicates multifaceted KT approaches are more effective than dissemination alone encouraging adoption of and implementation of new research, changing clinical outcomes and achieving improvements in policy and practice. The KT strategies used in this study were designed as a package rather than tailor made to specifically counter the barriers identified through the barriers and facilitators survey. It's confusing for the reader to clearly understand how the authors differentiate between the effects of the KT strategies the researcher team implemented in the study and the quality improvement processes implemented by each of the participating sites to facilitate practice change and improve use of MgSO4. Clearly the authors associate the change with their KT bundle based on the ITS analysis. But the piece that is missing here is to understand what happened following implementation of the KT strategies. By not taking into consideration the user response effort required, the site specific barriers that were identified and how they were addressed it appears that all sites were exposed equally and
responded equally - there's no information provided about how the KT interventions were 'managed' or tailored to address site specific barriers to practice change to understand what really happened? An important point for discussion and directly related to the term 'managed KT' that the authors use in the introduction. What was managed by the research team versus what tailoring happened to meet the needs of each of the participant sites based on the barriers survey?

We have changed ‘managed KT’ to KT strategy or intervention for better clarity.

We designed a central package that included guidelines, e-learning module, and local resources (such as pre-printed orders) as a starting point for local KT teams. The Barriers & Facilitators surveys were then designed to help the local sites identify how the central package should be adapted to their local environment, and how they were doing was illustrated by audit and feedback, including site visits, monthly teleconferences, e-mail contact for support. Also, we developed further resources as requested by the local team for local use, such as decision-aid tools and reminders for use in medical charts. If we refer to Table S7, we can see that all sites were not exposed and did not respond equally. Our user response to the initial year of KT was qualitatively analysed in our previous publication [Teela et al 2015].

Limitations: The authors acknowledge three limitations of this project: * Site investigators had to report local KT activities raising the possibility that some activities affecting MgSO4 may have been over-reported or missed. * Although the sample size of women was large overall, when examining the effects within individual sites, the study lacked power to determine the effectiveness of the KT strategies that were tracked. * Variability in application of some of the KT strategies - some were applied at the same time across all centres (i.e., the SOGC guidelines, the e-learning module, and invitations to central MAG-CP activities, such as newsletters and monthly teleconferences); however, other aspects were applied at non-random times across sites (such as site visits and local rounds).

* Recommendations: Additional limitations

- Lack of fidelity measures to verify whether the KT strategies were implemented as intended - which is a different question than whether participants reported using, accessing or attending something.

- Because there is no justification of the KT strategies used, and no confirmation that the strategies were implemented as intended across all sites - it is difficult to determine whether the change in practice reported was due to the full 'KT bundle' or to specific components of the bundle.
- Potential implications for social desirability and respondent bias to influence your barriers survey results.

We have clarified in our manuscript (as discussed above) that we did have measures of implementation fidelity, and did not collect only information on potential moderators of the intervention-adherence relationship, such as subject responsiveness. We agree, however, that we were unable to relate those measures to outcome, so we were unable to identify the components that were responsible for the increase in optimal use of MgSO4 for fetal NP; we have made this point clearly in the limitations. It is however possible that these KT strategies worked synergistically rather than the sum of effects by its individual components.

We question the assertion that the B&F survey may have been affected by social desirability. This was anonymous and in fact, the B&F survey yielded more comments about social-level barriers than did face-to-face discussions at the site visits [Teela 2015].

Overall Impression: Overall, this manuscript addresses an important issue in healthcare and is generally well written. The results of the ITS analysis are significant. My biggest issue is related to lack of completeness and transparency in reporting. Based on the StaRI (Standards for Reporting Implementation Studies) guidelines there are substantial issues related to the content as presented. This was an extensive study and I feel the paper warrants a place in the peer-reviewed literature. I would support it being accepted for publication in Implementation Science with the major modifications recommended above to enhance the information presented and strengthen the content. If revised, this paper could be a valuable resource for clinicians, decision makers and researchers interested in practice change as well as those involved in the provision of perinatal care.

Many thanks for your careful review and detailed suggestions. We have worked to address all and believe that this has strengthened the paper.

Thank you for the opportunity to review this paper.
REFERENCES


