Author’s response to reviews

Title: Application of Protection Motivation Theory to Clinical Trial Enrolment for Pediatric Chronic Conditions

Authors:

Stephanie Brooks (skowal@ualberta.ca)

Tania Bubela (tbubela@sfu.ca)

Version: 1 Date: 12 Dec 2019

Author’s response to reviews:

Responses to reviewer 1

Thank you to reviewer 1 for your kind words, enthusiasm for our work, and thoughtful feedback. We have responded to your comments in turn below.

1) Suggest in your Table 1, inclusion of parental perception of the child’s current ability to cope with their health condition (if known), as your results suggests that those who were coping better were less likely to enroll in the hypothetical study.

Thank you for this comment. We considered this point at length as we asked each parent about their child’s ability to cope at the beginning of each interview. This provided some categorical data. Most T1D parents said their child could cope, although with difficulty. In IRD nearly half of parents said their child was less able to cope. However, disease manageability is a spectrum and it was a very small number of exceptionally difficult conditions (e.g. co-morbidities or rapidly progressing blindness that children could not develop coping skill fast enough to ensure a quality of life) that stated they would consider assuming trial risks based on their child’s ability to cope. Including categorical data on this element of our findings overrepresented those children who were less able to cope and we could not represent the required nuance.

2) In your study, did parents offer any suggestions about how to improve the consent process (apart from their wish to speak to the CI)?

They did not. Our study design was more focused on the trial information provided and what level of risk the parents would accept. The finding about speaking to the CI was their way of clarifying questions and concerns they had when reading through the hypothetical cases. We did not ask questions about informed consent processes specifically and most parents had not had prior experiences with trials so they did not offer suggestions on the process itself.

3) It would be also helpful to discuss how your new modified protection motivation theory differed from the previous protection motivation theory, and how you derived the new model (what made you chose to make those changes?)
Our modifications were informed by the interview data that did not fit the existing PMT constructs. Additional constructs were added to allow the theory to incorporate complexity of decisions such as the ones presented in this article. Other modifications were just to reduce jargon and clarify how PMT applies in a clinical trial context. We have clarified our approach to modification in the first paragraphs of the results section. We have also added a third figure (now Figure 2) to represent language modifications that did not deviate from the original function of the PMT constructs.

The beginning of the results section now reads, “Using the directed content analysis method, we modified PMT to account for the context of ATMP clinical trials for chronic, manageable, pediatric conditions (Figure 2). Our deductive coding enabled us to identify interview data aligned with existing PMT constructs. Our inductive coding then allowed us to modify PMT to better represent the constructs in a clinical trial context (e.g. ‘maladaptive response’ became ‘the case for not enrolling’) (Figure 2).

INSERT FIGURE 2 HERE
We added two additional constructs to explain nuanced dynamics in parental decision-making. These were hope and fear and their effects in the adaptive response. In a clinical trial context, the threat appraisal makes the case for not enrolling in a clinical trial. The child continues to live with T1D or an IRD and does not assume the risks associated with clinical trial participation. The coping appraisal makes the case for enrolling in a clinical trial, based on potential benefits weighed against potential risks and logistical barriers. Parents simultaneously conducted a threat appraisal and a coping appraisal when considering the potential risks and benefits of clinical trial participation for their children.

INSERT FIGURE 3 HERE”

Responses to reviewer 2
Thank you to reviewer 2 for your thoughtful review of this article. We appreciate your pointing out areas to improve conceptual and writing clarity. We have responded to your comments and included the resulting revisions in turn below.

1) The concluding sentence of the Abstract, which is also the concluding sentence of the manuscript, is odd and does not seem to follow from the study results. This sentence makes it sound as if the quality of parental decision making was in doubt and also that providers are in a superior position to judge (and therefore either trust or mistrust) parental decision making. I suggest rewording and staying more consistent with what the study actually found.
We have updated the sentence in both spots to better articulate our finding that parents wish to make the best decisions possible on behalf of their children. The sentence now reads, “Parents called for available safety data and fulsome communication processes that would enable them to make informed decisions about clinical trial enrolment on behalf of their children.”

2) Page 4: the description of T1D as requiring insulin delivery by injection or pump is overly simple. The T1D treatment regimen involves much more than this and can be quite burdensome.
We have revised the sentence to read, “T1D is managed by way of careful, constant monitoring and response to insulin levels with an insulin regimen delivered by injection or pump; IRDs are managed with environmental design of home and workspaces along with supportive aids for progressive visual impairment. Treatment regimens and/or accommodations for T1D and IRDs are accordingly burdensome for children and caregivers.”

3) Page 5: the reference to "sharing open access code" is not clear- what do the authors mean? To clarify the meaning we added the subsequent sentence, “Open access code is made available by developers under terms that allow it to be modified and broadly shared. Such community modification of automated insulin delivery systems by-passes the regulatory environment for safety and efficacy of medical devices.”

4) Page 5: The authors should say more upfront regarding what they mean by "unregulated clinics." We clarified by revising the sentence to read, “Similarly, families seek unproven stem cell “therapies” for chronic diseases, including IRDs, from unregulated, for-profit clinics around the world, which market directly to consumers (a trend known as stem cell tourism)” [18,19,20].”

5) There is a lack of clarity regarding the adaptation of PMT to this decision making context, which first came up on page 6 at the end of the Introduction. The authors mention that they adapted the PMT- how was it adapted and what was the rationale for the need for adaptation? When was it adapted? Did the results of the study inform adaptation (which is implied on page 8, at the beginning of the Results), or did the authors adapt it first and then fit the results to the adapted framework (which is implied at the end of the Introduction)? Following the directed content analysis method described in the data analysis section, we started our coding deductively using established PMT constructs. We simultaneously inductively added new codes for data that did not appropriately fit the original version of PMT. The modification was a response to data that required additional constructs to account for nuance or language updates. These updates provided clarity and contextualized to our study. To clarify our approach to modification we have made the following revisions:
• Please see response to point #3 for reviewer 1 for the explanation of how it was modified and the rationale for the modification.

• On page 6 we revised the end of the introduction to read, “Parental decision-making for enrollment in pediatric clinical trials for chronic manageable diseases offers a complex example for the application of PMT. We describe how study results informed modifications to the PMT. The modifications accounted for complexities in parental decisions about enrolling their children, who are living with chronic manageable diseases, in clinical trials of gene and stem cell interventions.

6) More detail is needed regarding recruitment methods. For example, at patient-focused conferences, were research flyers made available? Was a presentation given? Did the research team depend on potential participants to actively contact them? How many people received the flyers and how many newsletters were sent? How many parents declined participation once details of the study were given?
We have added details about the recruitment but unfortunately do not have the level of granularity you requested about how many people received communications. We also cannot say who declined once given the information because the information sheet was the initial form of contact for recruitment. The clarification of recruitment is as follows, “The organizations enabled us to recruit at patient-focused conferences/research days by providing us with information booths to connect with potential participants directly or by providing study information letters in registration packages at conferences that we could not attend personally. Organizations also informed potential participants of the study via their online communications channels (e.g. newsletters). Participants who contacted the study staff provided informed consent prior to being interviewed.” We have further referenced our recruitment method in the study limitations section.

7) The headings in the Results section are quite confusing. I suggest taking a look and revising for clarity. One example is that there is a header for "threat and coping appraisals," which contains one sub-header for "fear." Then there are separate headers for "threat appraisals" and "coping appraisal." Several of the sub-headers that fall under "coping appraisal" don't seem like they belong under this header. Also, the header for "protection motivation" (page 15) doesn't make sense, as there was an earlier header for "modified protection motivation theory." Overall, the Results section could be revamped to be more concise. We revised the results to align with the modified PMT headings and the progression of steps in decision-making. This enabled us to fix the confusion caused by duplicative headings around appraisals. We have clarified what we mean by protection motivation, the construct, as opposed to modified protection motivation theory - the theoretical model as a whole. The revisions were too complex to show you in this response. Please review the results section to see the revisions. The results section is still long as this is a study of a complex theory, complicated by our comparison between T1D and IRDs. There are more illustrative quotes than a normal qualitative study for two reasons. First we wanted to accurately represent both parent groups. Second, we wanted the reader that parents in both chronic manageable disease groups made decisions using the same process. The results are long because of their comprehensiveness, but we think they are more clear and straightforward after responding to your suggestion to re-organize.

8) Page 17, first sentence of "treatment tourism" section: Is this sentence missing the word "not" between "would" and "enable"? We have corrected this typo. It now reads, “Most of the parents would not enable their child to receive unapproved therapies outside of the context of a credible clinical trial, including in a country with lower regulatory standards than North America or Europe.”

9) The Discussion needs more context (with references) for how these results show a distinction in this decision making context versus others. Also, differences between this study and studies of other contexts may have been impacted by the fact that this study explored responses to hypothetical trial enrollment, so the authors should be careful to not overstate their conclusions. We added 2 paragraphs for clarification of how our application differed from common applications of PMT. The beginning of the discussion section now reads, “Using the modified PMT, our results, when compared to those of other studies, demonstrated distinctions in decision-making processes between: a) preventative and treatment behaviors; b) acute/fatal diseases and chronic manageable conditions; and c) personal decisions versus those made on
behalf of someone else. Protective behaviours studied in health contexts are most commonly those to detect diseases (e.g. breast cancer screening), to adopt health practices (e.g. following an exercise regimen), or to cease unhealthy behaviours in response to acute or reversible disease threats (e.g. smoking cessation) (Milne et al. 2000, Floyd et al.2000). Clinical trial enrollment decisions are different in a number of fundamental ways.

Seeking treatment in general is an understudied behavior in PMT research (Floyd et al. 2000). To our knowledge, this is the first study applying PMT for those seeking experimental interventions. Furthermore, PMT literature often focuses on decisions to take up safe and healthy alternatives to poor existing health behaviours. Participants in our study viewed clinical trial enrollment is a potential alternative to living with T1D or and IRD but recognized the risks involved in experimental interventions.

Normally, response costs (trial risks in our PMT modification) represent beliefs about how costly performing the new protective behavior will be (Milne et al., 2000) (e.g. energy required to perform an action, comfort disclosing health information), however they are not normally risky themselves. Normally PMT is applied to situations where a person can continue with an unhealthy behavior or adopt a healthier path. Clinical trial contexts present a case for decisions between two risky paths containing uncertain outcomes. This is an exceptionally difficult type of decision to make on someone else behalf, especially when physical safety is at risk (Stone et al., 2013), as was the case for the parents in this study.”

10) Page 19: What do the authors mean by the appraisal of benefits impacting "other health behaviors”? More details are needed for this statement.
We expended on the concept of overcoming logistical barriers (self-efficacy in original PMT) to clarify that, “The ability to overcome logistical barriers is understood as a key component in all major health behavior models, including PMT [47], but our results suggest that, in a trial context, strong beliefs that the trial will create benefit negate logistical considerations.”

11) Page 20: The authors should provide a reference for the statement about this being "contrary to best practice."
It is standard practice in human-subjects health research and clinical trials to have a trial coordinator or study staff obtain consent. We have included reference to the TCPS2 which governs clinical research in Canada – e.g., Article 3.1 : on undue influence:
Undue influence and manipulation may arise when prospective participants are recruited by individuals in a position of authority. The influence of power relationships (e.g., employers and employees, teachers and students, commanding officers and members of the military or correctional officers and prisoners) on the voluntariness of consent should be judged from the perspective of prospective participants, since the individuals being recruited may feel constrained to follow the wishes of those who have some form of control over them. This control may be physical, psychological, financial or professional, for example, and may involve offering some form of inducement or threatening some form of deprivation. In such situations, the control exerted in a power relationship may place undue pressure on the prospective participants. At the extreme, there can be no voluntariness if consent is secured by the order of authorities.
REBs and researchers should also pay particular attention to elements of trust and dependency in relationships (e.g., between physician and patient or between professor and student). These relationships can impose undue influence on the individual in the position of dependence to participate in research projects. Any relationship of dependency, even a nurturing one, may give
rise to undue influence even if it is not applied overtly. There may be a greater risk of undue influence in situations of ongoing or significant dependency.

Pre-existing entitlements to care, education and other services should not be prejudiced by the decision of whether to participate in or withdraw from a research project. Accordingly, for example, a physician should ensure that continued clinical care is not linked to research participation. Similarly, where students do not wish to participate in research studies for course credits, they should be offered a comparable alternative.

12) Page 21: The authors should expand on how the recruitment method via patient advocacy organizations may impact the generalizability of the findings. We included a point in the study limitations section regarding recruitment and generalizability. It reads, “Further, we recruited participants who had a relationship with patient advocacy organizations; thus participants likely had an interest in clinical research and their views may not be representative of a general population of parents.”

13) Page 21: Do the authors mean to say, "We conducted individual interviews with parents…” (not patients)?
Yes, we have corrected this typo. The sentence now reads, “We conducted individual interviews with parents not with family units, including the children. Decisions to participate in clinical trials are unlikely to be made by individual parents.”

14) Table 1 needs revising. The row for "Total" under most categories is odd. Also, why not provide mean child age and SD/range instead of presenting it categorically? Why do numbers add up to more than the sample size for some of the variables?
Our organization and labelling of the table was indeed confusing. The varying totals reflect when we are describing parents (n=29) and when we were describing their children living with T1D or IRD (n=32). They do not match because three families had more than one child living with T1D or IRD. The totals were included to help people see the differences between the T1D and IRD subgroups. Similarly, categories gave a more appropriate picture of the variety of parental perspectives (e.g. parents with very young children compared to parents with teens). Please see revised table 1 in the revised manuscript.