PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a randomized trial of higher versus lower intensity patient-provider communication interventions to reduce antibiotic misuse in two pediatric ambulatory clinics in the United States
AUTHORS	Goggin, Kathy; Bradley-Ewing, Andrea; Myers, Angela; Lee, Brian; Hurley, Emily; Delay, Kirsten; Schlachter, Sarah; Ramphal, Areli; Pina, Kimberly; Yu, David; Weltmer, Kirsten; Linnemayr, Sebastian; Butler, C; Newland, JG

VERSION 1 – REVIEW

REVIEWER	François Angoulvant Hôpital Necker-Enfants Malades, Paris-Descartes University Paris, France
REVIEW RETURNED	01-Jan-2018

GENERAL COMMENTS	Manuscript ID: BMJ- 2016-020981, entitled " “Let’s talk about antibiotics”: A randomized trial of a higher vs. lower intensity patient-provider communication interventions to reduce antibiotic misuse in pediatric ambulatory clinics" I read with interest the protocol study by Kathy Goggin and colleagues describing a randomize cluster trial aiming to reduce inappropriate antibiotic prescription for ARTI. Providers (pediatrician and nurse practitioners) from two centers will be assigned to a higher intensity education arm or lower intensity education arm. Parent-child (1 to 5 years) dyads consulting for ARTI will be recruited. Quality of communication and satisfaction of care giver will be recorded. The main outcome is the inappropriate antibiotic prescription rate according to guideline. Major comments: This will be an original study on an important topic Major remark: • Main Outcome criteria: Pages 14-15: The author have chosen as main outcome criteria “inappropriate antibiotic prescription rate” which introduce a serious flaw in the study. Actions described page 15, do not eliminate the bias but merely check the consistency of providers: (medical records, diagnosis reached and announced to the parents, treatment). The clinical pertinent main outcome criteria should be the “antibiotic prescription rate for ARTI”. To illustrate this point, we can imagine the following results at the end of the study: As many antibiotic prescriptions in both arms, but less often considered inappropriate in one arm because more often related to a diagnosis of AOM. Rates of the different ARTI diagnosis should be described as secondary outcome. Some previous studies have shown that variation of diagnosis by providers have a

	tremendous impact on antibiotic prescription. Minors remarks: • Dates (planned) of the study should be included in the study according to the BMJ open instructions • Pages 9-10: It is unclear who will include the parent-child dyad and when and where this will occur: is it the provider? After having reach a diagnosis? it is crucial since the diagnosis have a deep impact on the main outcome criteria. • Page 14 “If the rates do not significantly differ, we will conclude that the lower intensity intervention is superior…”: NO, NO, NO failing to demonstrate a superiority is not an evidence of inferiority or equivalence. • The term “cluster” should be included in the abstract and in the trial design section (page 7)

REVIEWER	Michael Gionfriddo Center for Pharmacy Innovation and Outcomes, Geisinger, Forty Fort PA, USA
REVIEW RETURNED	25-Jan-2018

GENERAL COMMENTS	The authors report a protocol for a randomized trial or high vs. low intensity education and communication training interventions. The protocol is well written and complete. I suggest that the authors identify the report as a protocol in the title. I also identified a typo on page 11, line 7, I believe psychologist is incorrectly presented as the plural psychologists as well as a typo on page 12, line 37 "tri-fold" is missing the "f". Two additional minor comments: 1) Ensure Heading format consistent throughout article, see for example headings under data analysis (page 17, line 18) and 2) define CAB (page 16, line 30); several other abbreviations were not defined, but unsure if they are common enough to not need to be spelled out (e.g. CDC, UTI, HIV). Finally, I suggest the authors clarify how on page 12, line 54 how they will "ensure that any communications...do not reveal any of the strategies....". Unless I misunderstand, this does not seem feasible. That said, I feel the other stated strategies seem sufficient, especially if they are already monitoring a subset of visits to examine communication skills.

VERSION 1 – AUTHOR RESPONSE

Response to reviewer comments and editorial requests:

Editorial Requests:

- Please remove the quote from the title, correct the grammatical error and make it clear this is a study protocol. The study setting could also be more detailed here. We suggest: "Protocol for a randomized trial of higher versus lower intensity patient-provider communication interventions to reduce antibiotic misuse in three pediatric ambulatory clinics in the United States."

• We revised to use the suggested title, but have edited to “…two pediatric ambulatory clinics…” as that is a more accurate description. Our sites are 1) all four pods within a large academic pediatric medical center ambulatory clinic and 2) both locations of one much smaller pediatric private practice.

- Please remove the 'Conclusions' section from the abstract. The abstract should follow the guidelines provided in our instructions for authors for study protocols. See:

http://bmjopen.bmj.com/pages/authors/#study_protocols Please elaborate on your ethics approval statement in the abstract >> ethics and dissemination section. You should state the specific name(s) of the ethics committee(s) that approved your study along with the reference number(s).

• We have removed the 'Conclusions' section from the abstract and have elaborated on the ethics approval statement. The "Ethics/Dissemination" section of the abstract now reads: "Ethical approval was obtained from the Children's Mercy Hospital Pediatric Institutional Review Board (#16060466)."

- Please revise the 'Strengths and limitations' section on page 5. It needs to include some limitations as well as strengths.

• We have added the following limitation:
o "Provider training was limited to one 20-minute session for all providers and one additional 50-minute session for providers in the Higher Intensity arm."
• In order to keep to the maximum of five bullet points, we have combined the second and third strength from the original list. The second bullet point now reads:
o "Works closely with a multicultural group of parents, providers and other stakeholders to ensure feasibility and appropriateness of intervention components, study procedures, and study materials in Spanish and English."

- Please include an 'ethics and dissemination' section after the 'methods and analysis' section in the main manuscript, as per journal requirements for study protocols (see: http://bmjopen.bmj.com/site/about/guidelines.xhtml#studyprotocols)

• We have added an 'Ethics and dissemination" section after the 'methods and analysis' section, following the journal requirements. Please see pages 19-20.

- Re SPIRIT Checklist Item 13: Can you please include a schematic diagram in the paper as recommended by the SPIRIT guidelines?

• We now include a schematic diagram. Please see page 9 and Figure.

- Re SPIRIT Checklist Item 29: please clarify in the manuscript who will have access to the final trial dataset.
• We have clarified who will have access to the final trial dataset in the Ethics and dissemination section:

"A full data package will be maintained by the investigators at Children's Mercy Hospital for at least seven years after data collection is complete. Third-party access to the full data package will be addressed by Children's Mercy Hospital on a case-by-case basis."

- Please clarify where in the paper it states how personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (SPIRIT checklist item 27). We can't seem to find this information in the manuscript.

• We have added this information in the "Ethics and Dissemination" section:

"We will employ multiple strategies to protect confidentiality of personal information about potential and enrolled participants. Pre-screening of patients will be conducted exclusively by trained study staff on password protected computers and REDCap data collection tool. Appointments with potential participants will be flagged in electronic clinic scheduling systems accessible only to clinic and study

staff. Enrolled parent and patient participants will complete all measures in REDCap projects, which will only accessible to study staff who must use multiple passwords to access REDCap through the Children's Mercy network. Personal identifying information, namely medical record number and contact information, is marked as an identifier in REDCap and is then censored when the database is downloaded for analysis. All identifying information will be removed with the deletion of the REDCap project at the end of the study. Audio files of clinic visits will be stored in a password protected file on the Children's Mercy server that is only accessible to members of the study staff. Consent forms and signature logs for reimbursements will be secured in a locked file cabinet within a locked office on a secured floor."

- Please include the competing interests statement in a separate section on page 21 (rather than including it at the end of the acknowledgements).

• We have removed the competing interests statement from the acknowledgements section and have created a new section containing the statement.

Reviewer: 1

Major comments:
This will be an original study on an important topic Major remark:

• Main Outcome criteria: Pages 14-15: The author have chosen as main outcome criteria "inappropriate antibiotic prescription rate" which introduce a serious flaw in the study. Actions described page 15, do not eliminate the bias but merely check the consistency of providers: (medical records, diagnosis reached and announced to the parents, treatment). The clinical pertinent main outcome criteria should be the "antibiotic prescription rate for ARTI". To illustrate this point, we can imagine the following results at the end of the study: As many antibiotic prescriptions in both arms, but less often considered inappropriate in one arm because more often related to a diagnosis of AOM. Rates of the different ARTI diagnosis should be described as secondary outcome. Some previous studies have shown that variation of diagnosis by providers have a tremendous impact on antibiotic prescription.

• We will also report overall antibiotic prescription rates for different ARTI diagnoses by arm. Text added on pg 16, line 3.

Minors remarks:

• Dates (planned) of the study should be included in the study according to the BMJ open instructions

• We have added details on the planned dates in the manuscript. Please see pgs. 7, line -4 and 8, line 2.

• Pages 9-10: It is unclear who will include the parent-child dyad and when and where this will occur: is it the provider? After having reach a diagnosis? it is crucial since the diagnosis have a deep impact on the main outcome criteria.

• We describe that all potentially eligible parent-child dyads are screened and approached before the visit starts either in the waiting room or consulting room. Interested and eligible dyads are consented and baseline assessment is completed before they see their provider (please see, pgs 10 and 13). Providers have no role in identifying potentially eligible dyads, screening, consenting or data collection.

• Page 14 "If the rates do not significantly differ, we will conclude that the lower intensity intervention is superior…": NO, NO, NO failing to demonstrate a superiority is not an evidence of inferiority or equivalence.

• We have reworded the sentence to indicate that we will not conclude the lower intensity intervention is superior, rather, we will recommend it as preferable due to its lower cost and time burden. The sentence now reads: “If the rates do not significantly differ, we will conclude recommend the Lower Intensity intervention as preferable for dissemination, as its implementation requires less time and resources.”

The term “cluster” should be included in the abstract and in the trial design section (page 7)
• We have added the term “cluster” before the phrase “randomized trial” in both the abstract and the beginning of the trial design section.

Reviewer: 2

The protocol is well written and complete. I suggest that the authors identify the report as a protocol in the title.
• Thank you for the suggestion. We have revised the title to identify the article as a protocol. The title now reads: “Protocol for a randomized trial of higher versus lower intensity patient-provider communication interventions to reduce antibiotic misuse in two pediatric ambulatory clinics in the United States”.

I also identified a typo on page 11, line 7, I believe psychologist is incorrectly presented as the plural psychologists as well as a typo on page 12, line 37 "tri-fold" is missing the "f".
• Thank you, we have corrected.

Two additional minor comments: 1) Ensure Heading format consistent throughout article, see for example headings under data analysis (page 17, line 18)
• Thank you for pointing out the inconsistent heading format. We have applied our sub-heading format to the data analysis section, and changed the order of two sub-sections to improve flow.

2) define CAB (page 16, line 30); several other abbreviations were not defined, but unsure if they are common enough to not need to be spelled out (e.g. CDC, UTI, HIV).
• We deleted this single instance of the abbreviation ‘CAB’ and spelled out the full name “community advisory board”. We have also spelled out CDC and UTI.

Finally, I suggest the authors clarify how on page 12, line 54 how they will "ensure that any communications...do not reveal any of the strategies....". Unless I misunderstand, this does not seem feasible. That said, I feel the other stated strategies seem sufficient, especially if they are already monitoring a subset of visits to examine communication skills.
• We have clarified that we will “…train study team members to ensure that all of our communications (written or in person) with providers in the Lower Intensity arm do not reveal any of the strategies from the Higher Intensity training,” (Please see pg 13, line 1.)

VERSION 2 – REVIEW

REVIEWER	Francois Angoulvant Hopital Necker-Enfants Malades, Paris, France
REVIEW RETURNED	16-Mar-2018

GENERAL COMMENTS	The authors have modified their manuscript as requested. My only suggestion is to add the following sentence in the method section "Providers have no role in identifying potentially eligible dyads, screening, consenting or data collection."