

Fecal microbiota transplantation

Draft evidence report: Peer review

September 30, 2016

Health Technology Assessment Program (HTA)

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RESPONSES TO PEER REVIEWS AND PUBLIC COMMENTS

Spectrum Research is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all comments received during the public comment periods are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

This document responds to clinical and peer reviews from the following parties:

1. Christina Surawicz, MD (peer reviewer)
2. Paul Pottinger, MD (peer reviewer)

No other comments were received.

Specific responses pertaining to each comment are included in Table 1.

| Page of draft report (section) | Comment | Response |
|---|--|--|
| Christina Surawicz, MD (peer reviewer) | | |
| Introduction | Overview of topic is adequate? Yes | Thank you for your comments. |
| | Topic of assessment is important to address? Yes | |
| | Public policy and clinical relevance are well defined? Yes | |
| Background | Content of literature review/background is sufficient? The background and literature on rx of CDI and IBD was very flawed. I have edited and updated and will attach separate Word documents. | Thank you for your suggestions; we have looked them over and made a number of changes to the background section. |
| | Also p 44, collagenous and lym colitis are not types of IBD, this should be deleted. Also can add second peak of IBD in older individuals | |
| | P 41 definition of recurrence is wrong, do not need to have 6-8 wk taper, that is outdated. Also note that recurrent and refractory are different, I have clarified that in the word document. | |
| Report objectives & key questions | Aims/objectives clearly address relevant policy and clinical issue? Yes | |
| | Key questions clearly defined and adequate for achieving aims? Yes | |
| Methods | Method for identifying relevant studies is adequate? Yes | Thank you for your comments. |
| | Criteria for the inclusion and exclusion of studies is appropriate? Yes | |
| | Method for Level of Evidence (LoE) rating is appropriate and clearly explained? Yes | |
| | Data abstraction and analysis/review are adequate? Yes | |
| Results | Amount of detail presented in the results section appropriate? Yes | Thank you for your comments. |
| | Key questions are answered? One thing that can be confusing is the difference between recurrent and refractory, for instance the Cammarota study clearly had much more sick pts in it, with the pseudomembranes, so sick that the first 2 died which is why they changed the protocol. But for purposes of this review, it does make sense to combine those 2 RCTs. | |
| | Note new RCT from Kelly in Annals Intern Med August 2016 also positive. | The search was repeated on September 2, 2016 to identify new RCTs published since the original search date; the RCT by Kelly et al. (2016) was identified and has been included in the final report. |
| | If you want to add focus on severe/refractory the | Thank you for your comments. |

| Page of draft report (section) | Comment | Response |
|---|---|--|
| <i>Christina Surawicz, MD (peer reviewer)</i> | | |
| | <p>series of Monika Fischer should be included. The indications for FMT in this group are unclear so prob better to exclude.</p> <p>Also the evidence that FMT causes is flares of IBD is good so I would state this more strongly</p> <p>Figures, tables and appendices clear and easy to read? Yes</p> <p>Implications of the major findings clearly stated? Not really stated</p> <p>Have gaps in the literature been dealt with adequately? Yes</p> <p>Recommendations address limitations of literature? Yes</p> | |
| Conclusions | <p>Are the conclusions reached valid? Yes with the 2 following suggestions</p> <p>KQ1: <u>Your text:</u> Moreover, FMT procedure(s) for treatment of recurrent CDI (after the initial allocated treatment) were performed in significantly fewer patients in the FMT group than in the vancomycin group</p> <p><u>My comment:</u> This is confusing. What you mean to say is that since there were more people with recurrences in the vanco group, more of them had to have a “rescue” or repeat FMT.</p> <p>KQ3: <u>Your text:</u> quality of evidence was insufficient to draw no firm conclusions can be drawn.</p> <p><u>My comment:</u> My comment: the quality of evidence was insufficient to draw a firm conclusion. Is this what you mean to say?</p> | <p>Thank you for your comments.</p> <p>Thank you for your comment; the text has been edited for clarity.</p> <p>Thank you for your comment; the text has been corrected.</p> |
| Overall presentation and relevancy | <p>Is the review well-structured and organized? Yes</p> <p>Are the main points clearly presented? Yes</p> <p>Is it relevant to clinical medicine? Definitely yes</p> <p>What is surprising is that the treatment that is so effective clinically , ie FMT for RCDI, has low quality evidence and that the treatment that should be only</p> | <p>Thank you for your comments.</p> <p>Thank you. Yes, the overall quality evidence rating of low results from a combination of flaws in methodological design of the trials together with small sample sizes.</p> |

| Page of draft report (section) | Comment | Response |
|---|--|--|
| Christina Surawicz, MD (peer reviewer) | | |
| | <p>done in RCTs in my opinion has moderate quality of evidence. I assume this is because of flaws in the RCTs of the former. Clinically, this therapy for RCDI is so effective, and there is nothing else as good since the only other option for pts with multiple recurrences is to stay on vanco for the rest of their lives. I am not sure that this is clear in the report. FMT is the most successful therapy for RCDI, I started doing it in 2004, and would not have continued if not for the efficacy and for lack of other options.</p> <p>Is it important for public policy or public health? I am not sure that it is.</p> <p>Also note in the references, that reference #37 in the first set of references is incorrect and that ref.#35 in the second set is wrong, they are orthopedic papers.</p> | Thank you, these references have been removed. |
| Quality of the report | <hr/> <p><i>Quality Of the Report</i></p> <p>Superior <input checked="" type="checkbox"/> <input checked="" type="checkbox"/></p> <p>Good <input type="checkbox"/></p> <p>Fair <input type="checkbox"/></p> <p>Poor <input type="checkbox"/></p> <hr/> | |

| Page of draft report (section) | Comment | Response |
|---|--|------------------------------|
| Paul Pottinger, MD (peer reviewer) | | |
| Introduction | <p>Overview of topic is adequate? Yes</p> <p>Topic of assessment is important to address? Yes</p> <p>Public policy and clinical relevance are well defined? Yes</p> <p>This topic is clearly one of great importance to the health of Washingtonians (indeed, patients and their families nationwide), and this is made clear in the introduction.</p> | Thank you for your comments. |
| Background | <p>Content of literature review/background is sufficient? Yes.</p> <p>The background information is clear and easy to understand.</p> | |
| Report objectives | Aims/objectives clearly address relevant policy and | |

| Page of draft report (section) | Comment | Response |
|---|--|--|
| Paul Pottinger, MD (peer reviewer) | | |
| & key questions | clinical issue? Absolutely yes | |
| | Key questions clearly defined and adequate for achieving aims? Yes, very clearly. I am very impressed with the scope and technique employed here. | |
| Methods | Method for identifying relevant studies is adequate? Yes, totally. | Thank you for your comment. |
| | Criteria for the inclusion and exclusion of studies is appropriate? Yes (with note that a relevant study has been published since the time of this review, by Kelly et al, Ann Int Med 2016. If possible, that study should be included in the final draft). | The search was repeated on September 2, 2016 to identify new RCTs published since the original search date; the RCT by Kelly et al. (2016) was identified and has been included in the final report. |
| | Method for Level of Evidence (LoE) rating is appropriate and clearly explained? Yes. | Thank you for your comments. |
| | Data abstraction and analysis/review are adequate? Yes, very clear and exhaustive. | |
| Results | Amount of detail presented in the results section appropriate? Yes, more than I would have expected. | Thank you for your comments. |
| | Key questions are answered? Yes. | |
| | Figures, tables and appendices clear and easy to read? Very clear and easy to read. | |
| | Implications of the major findings clearly stated? Yes certainly. | |
| | Have gaps in the literature been dealt with adequately? Yes I think so; there are still unknown factors in this science, as is true in all areas of science, but you have made these perfectly clear. | |
| | Recommendations address limitations of literature? Yes, very clearly. | |
| Conclusions | Are the conclusions reached valid? Yes, I agree with the conclusions 100%. | Thank you for your comment. |
| Overall presentation and relevancy | Is the review well-structured and organized? Stunningly well organized and written. | Thank you for your comments. |
| | Are the main points clearly presented? Totally clear. | |
| | Is it relevant to clinical medicine? Yes absolutely, this | |

| Page of draft report (section) | Comment | Response |
|---|--|------------|
| Paul Pottinger, MD (peer reviewer) | | |
| | <p>issue arises in my medical practice virtually every week.</p> <p>Is it important for public policy or public health? Yes it is of huge importance, we need to reduce costs and reduce human suffering by increasing access to this safe, proven, effective technology.</p> <p>My overall comments are that this report is striking in its organization, clear in its methods and conclusions, and a pleasure to read. I hope there is a way for the authors to share this report with their counterparts in other States, to save them the cost and effort of repeating what is essentially a flawless product.</p> <p>My only thought for the future—not to detract from this report, but to place another technique on your agenda down the line—is to consider looking at the evidence supporting an alternative technique of treating the same syndrome by delivering dessicated stool via oral capsules. A rising body of literature suggests that this technique may be a safe, effective option for a subset of recurrent CDI patients, and it is one that should in fact be more affordable because colonoscopy is not necessary, and should be more tolerable because nasogastric tubing is not used. This emerging body of literature does not replace the need for current techniques, but may become an attractive option in certain circumstances in the very near future.</p> | |
| Quality of the report | <hr/> <p><i>Quality Of the Report</i> (Click in the gray box to make your selection)</p> <hr/> <p>Superior <input checked="" type="checkbox"/> <input checked="" type="checkbox"/></p> <p>Good <input type="checkbox"/></p> <p>Fair <input type="checkbox"/></p> <p>Poor <input type="checkbox"/></p> <hr/> | Thank you. |



**Comprehensive Evidence-Based Health Technology Assessment
Peer Review Form**

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for hip resurfacing. Your contribution and time are greatly appreciated.

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to robin@specri.com

If you have questions or concerns please contact Robin Hashimoto, PhD at the email above.

From Christina Surawicz

Sept 13, 2016

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate? YES
- Topic of assessment is important to address? YES
- Public policy and clinical relevance are well defined? YES

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient? THE BACKGROUND LITERATURE ON RX OF CDI AND IBD WAS VERY FLAWED. I HAVE EDITED AND UPDATED AND WILL ATTACH SEPARATE WORD DOCUMENTS.
- ALSO P 44, COLLAGENOUS AND LYM COLITIS ARE NOT TYPES OF IBD, THIS SHOULD BE DELETED. ALSO CAN ADD SECOND PEAK OF IBD IN OLDER INDIVIDUALS
- P 41 DEFINITION OF RECURRENCE IS WRONG, DO NOT NEED TO HAVE 6-8 WK TAPER, THAT IS OUTDATED. ALSO NOTE THAT RECURRENT AND REFRACTORY ARE DIFFERENT, I HAVE CLARIFIED THAT IN THE WORD DOCUMENT.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue? YES
- Key questions clearly defined and adequate for achieving aims? YES

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate? YES
- Criteria for the inclusion and exclusion of studies is appropriate? YES
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained? YES
- Data abstraction and analysis/review are adequate? YES

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate? YES
- Key questions are answered? ONE THING THAT CAN BE CONFUSING IS THE DIFFERENCE BETWEEN RECURRENT AND REFRACTORY, FOR INSTANCE THE CAMMAROTA STUDY CLEARLY HAD MUCH MORE SICK PTS IN IT, WITH THE PSEUDOMEMBRANES, SO SICK THAT THE FIRST 2 DIED WHICH IS WHY THEY CHANGED THE PROTOCOL. BUT FOR PURPOSES OF THIS REVIEW, IT DOES MAKE SENSE TO COMBINE THOSE 2 RCTS.
- NOTE NEW RCT FROM KELLY IN ANNALS INTERN MED AUGUST 2016 ALSO POSITIVE.
- IF YOU WANT TO ADD FOCUS ON SEVERE/REFRACTORY THE SERIES OF MONIKA FISCHER SHOULD BE INCLUDED. THE INDICATIONS FOR FMT IN THIS GROUP ARE UNCLEAR SO PROB BETTER TO EXCLUDE.
- ALSO THE EVIDENCE THAT FMT CAUSES IS FLARES OF IBD IS GOOD SO I WOULD STATE THIS MORE STRONGLY
- Figures, tables and appendices clear and easy to read? yes

- Implications of the major findings clearly stated? Not really stated
- Have gaps in the literature been dealt with adequately? Yes
- Recommendations address limitations of literature? Yes

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid. YES WITH THE 2 FOLLOWING SUGGESTIONS
- KQ1.
 - Your text: Moreover, FMT procedure(s) for treatment of recurrent CDI (after the initial allocated treatment) were performed in significantly fewer patients in the FMT group than in the vancomycin group
- - My comment : This is confusing. What you mean to say is that since there were more people with recurrences in the vanco group, more of them had to have a “rescue” or repeat FMT.
- KQ3
 - Your text” quality of evidence was insufficient to draw no firm conclusions can be drawn.
 - My comment: the quality of evidence was insufficient to draw a firm conclusion. IS THIS WHAT YOU MEAN TO SAY?
-

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized? YES
- Are the main points clearly presented? YES
- Is it relevant to clinical medicine? DEFINITELY YES, SEE BELOW
- Is it important for public policy or public health? I AM NOT SURE THAT IT IS.
-

WHAT IS SURPRISING IS THAT THE TREATMENT THAT IS SO EFFECTIVE CLINICALLY , IE FMT FOR RCDI, HAS LOW QUALITY EVIDENCE AND THAT THE TREATMENT THAT SHOULD BE ONLY DONE IN RCTS IN MY OPINION HAS MODERATE QUALITY OF EVIDENCE. I ASSUME THIS IS BECAUSE OF FLAWS IN THE RCTS OF THE FORMER. CLINICALLY, THIS THERAPY FOR RCDI IS SO EFFECTIVE, AND THERE IS NOTHING ELSE AS GOOD SINCE THE ONLY OTHER OPTION FOR PTS WITH MULTIPLE RECURRENCES IS TO STAY ON VANCO FOR THE REST OF THEIR LIVES. I AM NOT SURE THAT THIS IS CLEAR IN THE REPORT. FMT IS THE MOST SUCCESSFUL THERAPY FOR RCDI, I STARTED DOING IT IN 2004, AND WOULD NOT HAVE CONTINUED IF NOT FOR THE EFFICACY AND FOR LACK OF OTHER OPTIONS.

ALSO NOTE IN THE REFERENCES, THAT REFERENCE #37 IN THE FIRST SET OF REFERENCES IS INCORRECT AND THAT REF.#35 IN THE SECOND SET IS WRONG, THEY ARE ORTHOPEDIC PAPERS.

QUALITY OF REPORT

Quality Of the Report

(Click in the gray box to make your selection)

Superior **X**

Good

Fair

Poor



**Comprehensive Evidence-Based Health Technology Assessment
Peer Review Form**

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for FMT. Your contribution and time are greatly appreciated.

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to robin@specri.com

If you have questions or concerns please contact Robin Hashimoto, PhD at the email above.

Review of Fecal Microbiota Transplantation monograph.

9/22/16

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INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate? Yes
- Topic of assessment is important to address? Yes
- Public policy and clinical relevance are well defined? Yes

This topic is clearly one of great importance to the health of Washingtonians (indeed, patients and their families nationwide), and this is made clear in the introduction.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient? Yes.
- The background information is clear and easy to understand.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue? Absolutely yes.
- Key questions clearly defined and adequate for achieving aims? Yes, very clearly.

I am very impressed with the scope and technique employed here.

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate? Yes, totally.

- Criteria for the inclusion and exclusion of studies is appropriate? Yes (with note that a relevant study has been published since the time of this review, by Kelly et al, Ann Int Med 2016. If possible, that study should be included in the final draft).
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained? Yes.
- Data abstraction and analysis/review are adequate? Yes, very clear and exhaustive.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate? Yes, more than I would have expected.
- Key questions are answered? Yes.
- Figures, tables and appendices clear and easy to read? Very clear and easy to read.
- Implications of the major findings clearly stated? Yes certainly.
- Have gaps in the literature been dealt with adequately? Yes I think so; there are still unknown factors in this science, as is true in all areas of science, but you have made these perfectly clear.
- Recommendations address limitations of literature? Yes, very clearly.

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid? Yes, I agree with the conclusions 100%.

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized? Stunningly well organized and written.
- Are the main points clearly presented? Totally clear.
- Is it relevant to clinical medicine? Yes absolutely, this issue arises in my medical practice virtually every week.
- Is it important for public policy or public health? Yes it is of huge importance, we need to reduce costs and reduce human suffering by increasing access to this safe, proven, effective technology.

My overall comments are that this report is striking in its organization, clear in its methods and conclusions, and a pleasure to read. I hope there is a way for the authors to share this report with their counterparts in other States, to save them the cost and effort of repeating what is essentially a flawless product.

My only thought for the future—not to detract from this report, but to place another technique on your agenda down the line—is to consider looking at the evidence supporting an alternative technique of treating the same syndrome by delivering dessicated stool via oral capsules. A rising body of literature suggests that this technique may be a safe, effective option for a subset of recurrent CDI patients, and it is one that should in fact be more affordable because colonoscopy is not necessary, and should be more tolerable because nasogastric tubing is not

used. This emerging body of literature does not replace the need for current techniques, but may become an attractive option in certain circumstances in the very near future.

QUALITY OF REPORT

Quality Of the Report

(Click in the gray box to make your selection)

Superior

Good

Fair

Poor
