PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Development of a core outcome set for clinical trials in inflammatory bowel disease: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey
AUTHORS	Ma, Christopher; Panaccione, Remo; Fedorak, Richard; Parker, Claire; Khanna, Reena; Levesque, Barrett; Sandborn, WJ; Feagan, BG; Jairath, Vipul

VERSION 1 - REVIEW

REVIEWER	Claudio Romano Pediatric Department University of Messina Italy
REVIEW RETURNED	09-Apr-2017

GENERAL COMMENTS	The authors have adopted a new methodology for the selection of scientific papers in the context of IBD. The study design is appropriate. It would be useful to to change something to the conclusions extending certain clinical aspects (safety of biologics, strategies for prevention of infections and surgical risk)

REVIEWER	David Gracie Leeds Teaching Hospitals NHS Trust, UK. LIBACS, University of Leeds, UK.
REVIEW RETURNED	17-Apr-2017

GENERAL COMMENTS	Ma and colleagues provide a protocol for an exploratory study attempting to identify a novel set of core outcomes that will may, potentially, improve the relevance of outcomes reported in clinical trials in IBD. There is relative consensus among IBD researchers that the hitherto frequently adopted symptom based outcome measures reported in IBD clinical trials are inadequate. The proposed study is, therefore, welcome. There are a few points that are worthy of consideration: 1) The FDA approved use of PROs is not without limitation and integration of such endpoints into the COS should be included with caution. PROs are defined as “any report that comes directly from a patient about a health condition or its treatment, without interpretation of the patient's response by a clinician or anyone else”. As such, symptom scores are still likely be utilised, despite their poor sensitivity and specificity at predicting mucosal inflammation, particularly in CD (Targownik LE 2015 AJG).

	2) Please expand on the method of selection of clinicians for the Delphi survey. "Convenience sampling" is inadequate. 3) The number of researchers with 25 publications including 2 clinical trials or 1 systematic review of clinical trials will be significant. How will researchers be selected from this group? Again convenience sampling is inadequate. 4) Please expand on how "multi-national representation" of patients with IBD be achieved? Is there an international collaboration? The investigator affiliations are all North American. 5) The involvement of Pharma is poorly described. Could the authors expand on this? This would be welcomed given the exhaustive list of COIs that the authors declare. 6) American English is used throughout.....

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
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Reviewer: 1
Claudio Romano
Pediatric Department, University of Messina, Italy
****
Please leave your comments for the authors below
The authors have adopted a new methodology for the selection of scientific papers in the context of IBD. The study design is appropriate. It would be useful to change something to the conclusions extending certain clinical aspects (safety of biologics, strategies for prevention of infections and surgical risk)
Page 22, Lines 472-476, Ethics and Dissemination
• We thank Dr. Romano for these helpful comments. We agree completely that harmonization of safety outcome reporting in IBD clinical trials is a crucial component of this COS. Therefore, we have expanded the conclusions to highlight the salient clinical aspects, particularly with respect to reporting of treatment-specific adverse events and the need to develop preventative strategies to mitigate treatment risk

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Reviewer: 2
David Gracie
Leeds Teaching Hospitals NHS Trust, UK. LIBACS, University of Leeds, UK.
****
Please leave your comments for the authors below
Ma and colleagues provide a protocol for an exploratory study attempting to identify a novel set of core outcomes that will may, potentially, improve the relevance of outcomes reported in clinical trials in IBD. There is relative consensus among IBD researchers that the hitherto frequently adopted symptom based outcome measures reported in IBD clinical trials are inadequate. The proposed study is, therefore, welcome.

There are a few points that are worthy of consideration:

1) The FDA approved use of PROs is not without limitation and integration of such endpoints into the COS should be included with caution. PROs are defined as “any report that comes directly from a patient about a health condition or its treatment, without interpretation of the patient's response by a clinician or anyone else”. As such, symptom scores are still likely be utilised, despite their poor sensitivity and specificity at predicting mucosal inflammation, particularly in CD (Targownik LE 2015 AJG).

Pages 7, Lines 129-136, Introduction
• We thank Dr. Gracie for this very insightful comment. We agree that there are significant limitations to including PROs as treatment endpoints in IBD trials, if they end up being utilized as a primary endpoint without incorporation of an objective measure (e.g. configuration as a co-primary endpoint). The discordance between patient symptoms and objective disease activity is a central concern. We have included a paragraph in the Introduction emphasizing these limitations. Additionally, we have added the suggested reference.

2) Please expand on the method of selection of clinicians for the Delphi survey. "Convenience sampling" is inadequate.
Pages 17-18, Lines 365-369, Methods
• We aim to recruit global experts in IBD management, with both medical and surgical perspectives. Therefore, we will identify clinician leads from dedicated IBD centers from around the world. This strategy of recruiting clinical leads is similar to the strategy used by previous COS development programmes in gestational diabetes and otitis media (references provided).

3) The number of researchers with 25 publications including 2 clinical trials or 1 systematic review of clinical trials will be significant. How will researchers be selected from this group? Again convenience sampling is inadequate.
Page 17, Lines 363-365, Methods
• Similarly, to maximize expertise among Delphi panelists, we will preferentially invite lead and corresponding authors of clinical trials or systematic reviews.

4) Please expand on how "multi-national representation" of patients with IBD be achieved? Is there an international collaboration? The investigator affiliations are all North American.
Page 18, Lines 376-380, Methods
• Although the authors of this manuscript are all from North American affiliations, we have strong collaborative ties with IBD centers internationally and we will aim to recruit patients with IBD through this network and their representative patient bodies accordingly. We aim to recruit patients from different regions to achieve multi-national representation.

5) The involvement of Pharma is poorly described. Could the authors expand on this? This would be welcomed given the exhaustive list of COIs that the authors declare.
Page 18, Lines 376-380, Methods
• Since all successful drug development in IBD, and on-going clinical development, has been conducted by the pharmaceutical industry, it is essential to have involvement and ratification of a COS by industry stakeholders. We aim to limit pharmaceutical representation to approximately 10% of Delphi survey participants.

6) American English is used throughout.
• The manuscript has been edited for spelling and grammatical errors accordingly.

VERSION 2 – REVIEW

REVIEWER	David Gracie Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK LIBACS, University of Leeds, Leeds, UK.
REVIEW RETURNED	27-Apr-2017

GENERAL COMMENTS	Comments from previous review appropriately addressed in the main.