

For review article

Response to Reviewer 1 Comments

Summary

Thank you very much for taking the time to review this manuscript. Please find the detailed responses below and the corresponding revisions highlighted **in pink** in the re-submitted files.

Point-by-point response to Comment

Suggestions for Authors

Introduction Comment 1

: The introduction is brief. Some statements should be confirmed with references:

Line 58/9: 'Non-adherence in IBD leads to high healthcare and societal costs.'

[Kane & Shane 2008, doi 10.1007/s10620-007-9968-0] or [Park 2020, doi 10.1093/ibd104].

Response 1: Thank you for pointing this out. We agree with this comment. Therefore, we have confirmed this statement with the following references (Please see: Page 3, Paragraph 2, Line 59):

13. Selinger CP, Eaden J, Jones DB, Katelaris P, Chapman G, McDonald C, Smith P, Lal S, Leong RW, McLaughlin J, Robinson A. Modifiable factors associated with nonadherence to maintenance medication for inflammatory bowel disease. *Inflamm Bowel Dis*. 2013 Sep;19(10):2199-206. doi: 10.1097/MIB.0b013e31829ed8a6. PMID: 23899547.
52. Zand A, Nguyen A, Stokes Z, Van Deen W, Reynolds C, Dimitrova M, Khandadash A, Dvorsky M, Sauk J, Esrailian E, Hommes D. The development of a screening tool to identify and classify nonadherence in inflammatory bowel disease. *Crohn's & Colitis* 360. 2019;1(3). doi:10.1093/crocol/otz035
87. Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med* 2003, 114:39, 43.

Comment 2: Line 63-5: '*Several theories have been proposed as to why people are non-adherent to their medication, with recognition that some factors can be modifiable.*' Please tell us what these interesting theories say and provide the references.

Response 2: Thank you. We have elaborated upon these theories (please see, Page: 3, Paragraph: 2, lines: 63-70).

"Several theories have been proposed as to why people are non-adherent to their medication, with recognition that some factors can be modifiable and can be addressed. This includes health psychology, behavioural and cognitive theories^[101] (self-efficacy model, health belief model, social cognitive theory and theory of planned behaviour) which consider an individual's cognitions as key behaviour change factors. Alternatively, biopsychosocial models^[102,112] attribute various physical and psychosocial influencers to explain non-adherence, such as gender, side effects, forgetfulness or lack of treatment knowledge."

Referenced as follows:

- 101] Unni E, Bae S. Exploring a New Theoretical Model to Explain the Behavior of Medication Adherence. *Pharmacy* (Basel). 2022 Apr 1;10(2):43. doi: 10.3390/pharmacy10020043. PMID: 35448702; PMCID: PMC9025348.
- 102] Webb TL, Joseph J, Yardley L, Michie S. Using the internet to promote health behavior change: A systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. *J Med Internet Res*. 2010. 12(1):e4.
- 112] Jackson, CA; Clatworthy, J; Robinson, A; Horne, R. Factors Associated With Non-Adherence to Oral Medication for Inflammatory Bowel Disease: A Systematic Review. *American Journal of Gastroenterology* 105(3):p 525-539, March 2010. | DOI: 10.1038/ajg.2009.685

Comment 3: Line 57: check the brackets

Response 3: Thank you. The closing bracket has been made the correct size now and the comma follows after this. (Please see Page 3, Paragraph 2, Line 57):
"surgery^[6],"

Results Comment 4: *The problem of rectal administration deserves special mention in the introduction and/or discussion section [ECCO guidelines 2022, doi 10.1093/ecco-jcc/jjab178]. Also valuable [Boyle 2015, doi 10.1097/MIB.0000000000000562], [D'Inca 2008, doi 10.1111/j.1365-2036.2007.03555.x]*

Response 4: Thank you for this comment. This is referred to in the Discussion and referenced accordingly. (Please see page 28, paragraph 3, lines 668 – 670):
"IBD treatment administered via various routes^[85], may cause discomfort (e.g., injections, rectal medications or oral tablets difficult/ large to swallow) and be associated with greater non-adherence risk^[25,77], impacting life quality^[62]."

Comment 5: *Line 366ff: Specification of probability: I know p-value with small p*

Response 5: Thank you. My understanding of this comment is to amend p-values to a small p. This has been done as follows:

(Page 20, Paragraph 7, Line 395) *"(p<0.0001),"*
(Page 20, Paragraph 8, Line 403) *"(p<0.001),"*
(Page 20, Paragraph 8, Line 405) *"(p=0.049),"*

Discussion Comment 6: *Line 664/5: Special routes of administration are discussed very briefly '(e.g., injections, rectal medications or oral tablets difficult/ large to swallow)'. Rectal treatment, for example, is a specific challenge which could be discussed in more detail.*

Response 6: Thank you for this comment. Rectal treatment specifically was not found to be related to non-adherence in the studies reviewed. In fact, it was identified that when individuals had not previously used rectal treatment, they were more likely to be non-adherent to oral IBD treatment (Yen et al).

In line with your comments, the following statement has been added: (highlighted in pink, Page 31, Paragraph 4, Lines 761- 762)

"Interestingly, contrary to widespread opinions, this review did not find that rectal treatments were related to non-adherence."

Comment 7: *The statement in line 682/3 '...require hospital appointments for administration, raising non-adherence risks[22]' suggests a particularly high non-adherence for intravenous administration of biologics in hospital. Does Reference 22 support this statement? Passive administration in hospital differs considerably from active intake or independent use by patients.*

Response 7: Thank you for your comment. I can confirm that the qualitative Reference 22 supports the statement that treatment infusions can increase non-adherence as taking such medication is less of a habit, whilst requiring more effort, proactivity, time, travel and costs for some.

To reinforce that this is not a passive patient role the following statement has been amended to this section (see Page 28, Paragraph 5, Lines 686-687): *"require attendance to hospital for administration...."*

Comment 8: *The sentence 'Forward and backward translation prior use is therefore recommended.' in line 793/4 may be removed.*

Response 8: Thank you. This has been removed as advised.

