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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49807

Title: Individualized home-monitoring of disease activity in adult patients with inflammatory bowel disease can be recommended in clinical practice: A randomized-clinical trial

Reviewer's code: 02446483

Reviewer's country: Canada

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-06-25 11:14

Reviewer performed review: 2019-06-25 13:09

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript is an excellent report of data using modern technologies to track patients experiences. Inflammatory bowel disease (IBD) can be excessively stressful for patients and health care providers. In this clinical trial, Munkholm's group addressed a niche in

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the world of patients with IBD. Involving patients with IBD in their disease by home monitoring of disease activity, has been shown to bring IBD patients significantly faster in remission. The authors randomized 102 IBD patients to screen for disease activity either every third month or whenever the patients felt a need for screening on the ibd.constant-care.com web-application for one year. The authors found that the two screening procedures were equally good in capturing a relapse and bringing about remission. The authors may emphasize more the difference between children and adults.

Thank you for your comment on discussing the difference between pediatric/adolescents and adult IBD home-monitoring in the manuscript. Katrine Carlsen MD did her PhD 2018 in telemedicine/home-monitoring of pediatric and adolescent IBD using the web application young.constant-care.com. Carlsen and co-workers found that self-administered telemedicine reduces the number of outpatient visits, days of absence from school and further to empower pediatric and adolescent IBD patients. Pediatric IBD patients were instructed to screen for disease activity every month according to the disease algorithm consisting of Fecal Calprotectin and PUCAI or aPCDAI. They were further instructed to contact their IBD nurse or doctor as usual if it was necessary. There is no substantiating evidence of the screening protocol (once every months) for pediatric IBD patients and I know that they are looking forward with interest to the present results on adult eHealth screening protocol for IBD. In the discussion section in the manuscript line 377-379 there have been added the following: For children and adolescents, a fixed eHealth screening interval of once every month have been shown to be feasible. One could speculate if the OD screening approach could apply for pediatric IBD patients as well (Carlsen et al. 2017. Self-managed eHealth disease monitoring in Children and Adolescent with inflammatory bowel disease: A randomized controlled trial. IBD; 23:357-365, Ref 17 in the manuscript)

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49807

Title: Individualized home-monitoring of disease activity in adult patients with inflammatory bowel disease can be recommended in clinical practice: A randomized-clinical trial

Reviewer's code: 03478404

Reviewer's country: Romania

Science editor: Ruo-Yu Ma

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Reviewer performed review: 2019-06-30 09:37

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Telemedicine represents a modern concept in IBD and not only. In this manuscript, the authors reported results of adult patients with IBD using home self-monitoring of disease activity, by electronic health screening procedure for their disease activity, either every

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third month (3M) or according to patient own decision, on demand (OD). Both groups were screened not only by clinical indices of activity (in both UC and CD), but also by a validated fecal calprotectin home test. In addition, questionnaires regarding quality of life, fatigue and medical compliance were also included. Neither difference between groups was found regarding mean time spent in remission, overall relapse rates, time to a severe relapse and remission, nor regarding medical compliance, fatigue and quality of life. Only the median number of fecal calprotectin home-monitoring tests/patient was significantly higher in the 3M group, but it concerned mainly patients in the green zone (meaning remission). Given these outstanding results showing that the "On Demand" screening system to self-monitoring IBD is more cost-effective, this system was already implemented by authors in their area since June 2018 and it seems it is working very well. This system could be implemented in other centres too, leading to huge savings for the health care system, but also saving patients' time for medical visits. According to this study, patients were satisfied with the method. Title, Core-tip and background (including the authors' personal published experience regarding screening of disease activity using electronic health or mobile health applications and telemanagement) are appropriate. Material and methods are presented in detail, including study design and data analysis. Results are supported by figures and tables of excellent scientific quality and very illustrative. Discussion paragraph is well written, including strengths and limitations. Although I am not a telemedicine fan, I have to say this paper is very good and useful for practice.

Minor comments: 1. Please include among references (and discuss) the following: "Bossuyt P, et al. E-health in inflammatory bowel diseases: More challenges than opportunities? Dig Liver Dis. 2017;49(12):1320-1326.".

The reference has been included and discussed shortly in the manuscript, line 385: According to

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Bossuyt et al. 2017 one of the major concerns regarding implementation of eHealth in IBD is a less robust digital infrastructure that is not sufficiently workable for patients and healthcare providers. Although there might be room for improving the digital infrastructure, the Constant Care platform has in this study shown to be satisfactory from a patient perspective.

2. Lines 90-92: "Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory diseases of the gastrointestinal tract that result from interactions of the intestinal immune system and the gut microbiome[1]." Environmental factors should be included, as well as epigenetics, otherwise interactions are not correctly defined.

Epigenetics and environmental factors have been added to the sentence in the introduction section of the manuscript, Line 105-106.

3. Lines 105-106: "Close monitoring of disease activity is vital for optimizing Individualized treatments and to potentially improve the long-term disease course." Indeed, but mucosal healing is the standard aim of care and this home-monitoring does not allow to fulfil this aim. Many patients in clinical remission have endoscopic lesions and (in Crohn's disease) transmural lesions, including strictures and penetrating disease, without necessarily being symptomatic. Fecal calprotectin may be a surrogate marker for mucosal inflammation, but this is a valid option especially in ulcerative colitis, which is a mucosal disease. Crohn's disease is transmural and fecal calprotectin is less useful for small bowel disease. No exact information is therefore provided about mucosal (and eventually transmural) healing. Patients have to be examined clinically and endoscopically, ideally also by imaging techniques (especially in Crohn's disease), on a regular basis (i.e. every 3-6 months, depending on age, type of disease, complications and so on). These are my concerns regarding telemedicine, but the authors included those

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limitations in the Discussion paragraph. Maybe authors should insert that "this home-monitoring system is not the requested one by the existing guidelines".

We do acknowledge your concern and the fact that the home-monitoring disease algorithm does not include endoscopy and imagining, however, as you stated we have discussed that in the manuscript and furthermore IBD patients enrolled in the web-out patient clinic will undergo the same practice as standard care which means colonoscopy when need and at least every three to five years (ECCO guidelines for surveillance of CRC). This has been added to manuscript line 338.

4. Lines 112-117: Participants: inclusion criteria. Recruited patients were only in clinical remission or mild-to-moderate disease, according to clinical scores. Endoscopic and/or transmural activity of the disease were not assessed. Please explain.

All IBD patients had priori to inclusion and at diagnosis fulfilled the Copenhagen diagnostic criteria (ref. 2 and 3 in the manuscript). Thus, endoscopy and MRI have been carried out for all IBD patients enrolled in the study.

5. I wonder how many of these patients (in both arms) were examined endoscopically and/or by imaging techniques and found with important lesions (while being in clinical remission and having normal fecal calprotectin levels), AFTER THE END of the study.

We take your point, however, endoscopy at inclusion and end of the study was out of the scope of this study. However, in an earlier publication by Carlsen et al (The sensitivity of fecal calprotectin in predicting deep remission in ulcerative colitis. Scandinavian Journal of Gastroenterology, Vol. 53, No. 7, 2018, p. 825-830) they validated disease activity scores in UC patients.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49807

Title: Individualized home-monitoring of disease activity in adult patients with inflammatory bowel disease can be recommended in clinical practice: A randomized-clinical trial

Reviewer's code: 00054993

Reviewer's country: Austria

Science editor: Ruo-Yu Ma

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Review time: 2 Days and 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The criteria checklist can be answered in every point positive. In this randomized clinical trial the use of an electronic health screening procedure testing for disease activity in IBD on demand (n=50) or at fixed intervals of 3 months (n=52) was investigated prospectively

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over a period of 1 year. A total of 130 patients with IBD were assessed for eligibility, finally 88 patients completed the prospective study after one year. Authors could show the feasibility of eHealth home monitoring in IBD patients on conservative treatment (what has been shown and published earlier already). Even in elaborate analyses no differences between the two patient groups could be shown, except for the fact, that screening on demand needed significantly less fecal calprotectin test-kits per patient (4 kits instead of 6). On demand IBD activity screening therefore is recommended by the authors.

Major critique: Results apply for a highly selected group of patients in Denmark (Danish language mandatory) only with access to the world wide web and appropriate skills. Even out of this selected group only 88 of 130 screened patients came into final analysis (68%).

It is a highly selected group of IBD patients included either in remission or mild-to moderate activity, however, inclusion of patients in the study were not restricted by specific medical treatment steps. Patients with severe activity were excluded at baseline (18 patients, cf. figure 2) – a major reason why only 68% went into the final analysis. Availability of smartphones, access to the internet and digital health literacy might be obstacles, in particular, for the elderly suffering from IBD.

What are the costs for a CalproSmart test kit and how much money could be saved by the On Demand-screening procedure?

The price of a CalproSmart test kit is 35 Euros. A standard FC ELISA test here in Denmark costs approx. 42 Euros, which is a saving of approx. 7 Euros per test. Looking at the medians for FC tests only for the on demand (OD, 4 FC test per patient per year) and every third month (3M, 6 FC test per patient per year) screening protocol, the OD protocol will save approx. 14 Euros per IBD patient ever year. We are on our way with a subsequent analysis on health economics in eHealth (Ankersen et al 2020) and it will be published next year.

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