

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Internet- and mobile-based aftercare and follow-up for mental disorders: Protocol of a systematic review and meta-analysis
AUTHORS	Hennemann, Severin; Farnsteiner, Sylvia; Sander, Lasse

VERSION 1 - REVIEW

REVIEWER	Vandad Sharifi Tehran University of Medical Sciences, Tehran, Iran
REVIEW RETURNED	21-Mar-2017

GENERAL COMMENTS	<p>This is a protocol that describes the design and methods of a systematic review of the research conducted on the effectiveness of internet and mobile based interventions for the aftercare/followup of patients with mental disorders.</p> <p>The recent development of interventions by employing novel technologies shows promise that if effective can improve the lives of patients with mental disorders. Therefore it would be interesting to see what would be the effect of such interventions. However, I have some major concerns:</p> <ol style="list-style-type: none">1. First concern is the amount of heterogeneity that could be observed in the study. The target population constitutes all mental disorders, from mild depressive disorders to severe mental illnesses like schizophrenia. They have many dissimilarities with regard to their aftercare needs and for that purpose there could be quite diverse interventions. For example compare the aftercare needs of - and therefore suitable intervention for- patients with schizophrenia, with like followup psychosocial sessions for a mild depressive disorder after a course of CBT. This amount of heterogeneity is very important when pooling the data and meta-analysis are the main objectives of the review.In additions, What is the definition of convalescent patients (page 5)? Do the studies need to provide criteria for that, like some degree of improvement after initial care/treatment?2. The same heterogeneity could be observed for the "interventions." There should be clear definition for the "internet"and "mobile"based interventions. For example, does the mobile (cell phone) need to be connected to a network? Does that include voice , text message or phone calls? Does it include interventions using smartphones? The authors are going to include only "psychological interventions." Are interventions that foster adherence to treatments or followup visit (main components of any aftercare/followup intervention) considered a psychological intervention?3. The other concern would be the outcome measures. The most important outcomes for any aftercare of people with mental disorders, especially those with severe mental disorders, could be adherence to treatment and rehospitalization. None are considered as outcomes of interest.
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	<p>Another question would be why the authors have chosen symptom severity as the primary outcome. If they want to see the effect of these interventions as "tertiary prevention," the primary outcomes could be either recurrence rate or functionality of patients (or both) and symptom severity could be a secondary outcome.</p> <p>Minor comments:</p> <ol style="list-style-type: none"> 1. The researchers may want to include SCOPUS as another electronic source to improve the comprehensiveness of their search. 2. One additional search term could be "post-discharge."
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REVIEWER	<p>Sofian Berrouiguet Brest University Hospital IMT atlantique engineer school France</p>
REVIEW RETURNED	05-Apr-2017

GENERAL COMMENTS	<p>This papers describes the protocol of an interesting review aiming to review existing web and mobile apps for the tertiary prevention. Authors also propose to perform a meta-analysis of these datas, wich is an ambitious and promising task.</p> <p>The methods is described properly. However, i have some concerns about the insight that may provide the results of this study to researchers of this field:</p> <ol style="list-style-type: none"> 1. Authors states that no previous systematic review has investigated comprehensive evidence on IMIs, which is almost true. However, insight regarding the efficacy of these applications exists in other reviews that have others fields of mental Heath and described the same articles that wil include in this review the authors. Thus I suggest to strength the introduction section regarding existing reviews, especially proceeding from e-health specialized journals. it may healp readers to understand the contribution of this review regarding what has already been done. 2. The methods only focuses on clinical outomes. However, the topic is highly technical. The technical aspects of web and samrtphone based has to be adressed, as they represent a critical issue regarding the feasability and reproductibility of the interventions. Technical aspects are generally well described by e-Heath papers. These aspects should be added in secondary outcomes. <p>minor</p> <ol style="list-style-type: none"> 3. In the method section, data items sub heading, the following items could be added: <ul style="list-style-type: none"> -Language of the web app -patient or clinician acceptability (should be discussed in the discussion section) -technical aspects e.g. web app, smartphone, wearables (see above) -therapeutical method e.g CBT, reminders, informant....
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

---Majors---

1a) Comment: Heterogeneity in terms of mental disorders, aftercare implementation.

Answer: In line with your valuable comment on heterogeneity through inclusion of various mental disorders, objectives of aftercare and implementations of IMIs, we emphasized the expected dimension of heterogeneity and the requirements for meta-analysis in the homonymous section (p. 7):

‘The expected heterogeneity of studies in terms of clinical (e.g. mental disorder, intervention objective, type of IMI,) methodological (comparators, assessment methods) or statistical (e.g. comparability of outcome measures) will be considered carefully.’

Correspondingly, we included ‘study design, intervention type’ as indicators of heterogeneity in the section ‘methods’ of the abstract (p. 2) and in the section ‘Meta-Analysis’ (p.7).

Also we added the following bullet point to the section ‘strengths and limitations of this study’ (p. 2):

‘Heterogeneity of studies in terms of clinical, methodological or statistical aspects will be considered carefully.’

The primary aim of this review is to give a comprehensive overview. Meta-analytical pooling will only be performed if applicable with regard to above mentioned sources of heterogeneity.

1b) Comment: ‘convalescents’ misleading.

Answer: We agree, that the term ‘convalescent’ is unspecific and ambiguous. Thus, we decided to cross this term out and clarified eligibility criteria with ‘interventions following acute treatment’ (p. 5).

2a) Comment: Heterogeneity in terms of interventions: Definition of IMIs

Answer: According to your comment, we added an established definition of IMIs by the WHO, complemented by examples of the most common technical implementations and areas of application to map this broad area of modern interventions (p. 3):

‘(...) can be defined as “health related services and systems, carried out over a distance by means of information and communications technologies, for the purpose of global health promotion, dis-ease control and health care (...)”(p . 1). IMIs can be categorized by technical implementation (e.g. PC, Smartphone, Wearables), content (e.g. education, monitoring, behavior-change), localization in the health care process (e.g. prevention, stand-alone, aftercare), amount of human support (self-administered/automatized, self-help with minimal guidance, online-therapy) and therapeutic contact (e.g. E-Mail, SMS, Live-Chat/Video) [28]’

In the section ‘Study design and interventions’ under (h) we further specify inclusion criteria regarding technical implementation of IMIs (p. 5).

2b) Comment: Psychological Interventions

Answer: We thank you for this valuable comment. We agree, that monitoring and promotion of adherence to primary treatment are key aspects of most aftercare interventions. In an effort to specify and homogenize our study focus, we base our search on psychological intervention methods. These comprise differentiated, mostly modular and guided interventions for continuous care with a focus on stabilizing treatment effects or further reducing symptom severity. Therefore, we selected the latter as our primary outcome (see also comment 3). Furthermore, a preliminary screening of the literature

showed, that IMIs in medication adherence, cognitive remediation/rehabilitation represent a separate field of research that partially has been covered in previous reviews (e.g. MacDonald et al.,2016). However, in line with your comment, we included symptom monitoring and interventions promoting adherence in the inclusion criteria in the section 'Study design and interventions' (p.5).

'Interventions may contain symptom monitoring, promotion of adherence to primary treatment (e.g. medication compliance)'

And further specified in the same section (p.5):

'If symptom monitoring or reminders to treatment adherence are the predominant intervention modality, studies will only be included, if accompanied by a distinguishable psychological intervention element.'

Also, in the introduction we included meta-analytic evidence on interventions improving medication adherence in mental disorders (p. 3):

'(...) and promoting functionality or medication adherence [18,19] in mental disorders following acute treatment.'

Furthermore, we included the specification 'psychological' to the IMIs under study in the section 'Objectives' of the abstract (p. 2) and in the introduction (p. 4).

3. Comment: Outcome Measures

Answer: We thank you for your considerate comment. Symptom severity was chosen as primary outcome since (a) it's significance in patient's subjective evaluation of well-being, (b) to account for the dimensional aspect of mental disorders in which symptoms fluctuate and traverse along a continuum rather than binary states, being a key foundation of in-/outpatient treatment rationales and (c) since preliminary searches demonstrated that the RCTs under study consistently report symptom severity on basis of validated questionnaires as indicator of maintenance of treatment effects. We believe, this strategy will yield rather homogeneous results than a more 'conservative' criterion like recurrence rate as primary outcome. Therefore we suggest 'symptom severity' as primary outcome and according to your highly appreciated comment a more differentiated secondary outcome. In the section 'Outcomes and prioritization', (p. 7) we therefore included your suggestions:

'(c) rehospitalization rate, (d) indicators of functionality or quality of life and (e) adherence to primary treatment (e.g. medication compliance)'

as well as in 'data items' under 'clinical outcome' (p. 6).

'(j) clinical outcome (symptom severity, /recurrence rate, rehospitalization, functionality, quality of life, adherence to primary treatment).'

From your comment, we also concluded, that the term 'tertiary prevention' is rather ambiguous. Hence, we more precisely defined 'aftercare' and 'follow-up' measures as the main focus of this review and use the former over the latter. We thus separate more clearly between aftercare interventions and disease management or 'stand-alone' interventions for chronic or recurrent diseases. Thereby we clarify inclusion of studies following acute treatment (see 'Eligibility criteria' subsection 'Population' (p. 4) and 'Study design and interventions' under (g), p.5). In the abstract, subsection 'introduction' (p. 2) we highlighted the vulnerability of the post-discharge phase and importance of aftercare measures and added the following text:

'Thus in the vulnerable post-discharge phase, aftercare (e.g. rehabilitation, follow-up, maintenance treatment) (...) thus aims at stabilizing treatment effects (...)'

Here, we crossed out the term 'tertiary prevention'. This also applies to the main introduction, where we clarified focus on aftercare and replaced 'tertiary prevention' by 'aftercare' (p. 3, 4) or 'aftercare instruments' in the 'Objectives' section (p. 4). In the latter, we formally corrected the bracket with examples, adding the term 'maintenance-'.

Consequently, we crossed out the specification 'tertiary prevention of (...)' in the title to allow for focusing on aftercare instruments in mental disorders. The adapted title will be:

Internet- and mobile-based aftercare and follow-up for mental disorders: Protocol of a systematic review and meta-analysis

And:

'Internet- and mobile-based interventions may represent low-threshold and effective extensions to aftercare interventions in tertiary prevention of mental disorders.'

---Minors---

1. Comment: Inclusion of SCOPUS

Answer: We thank for the recommendation. Although SCOPUS represents an interdisciplinary and extensive data base, we are confident in the exhaustion of the present data bases not only in the field of mental disorders but also as leading databases with regard to telemedicine and eHealth. We carefully selected these on basis of a previous extensive review we performed on prevention of mental disorders through IMIs (Sander, Rausch & Baumeister, 2016) and further significant reviews in this field which are quoted in the introduction (e.g. Richards & Richardson, 2012, Nieuwenhuijsen et al., 2014, Olthuis, Watt, Bailey, Hayden, & Stewart, 2015). Thus we suggest the retention of the present databases.

2. Comment: Add 'Post-discharge' in search string

Answer: We thank you for this helpful suggestion and included the term in our search string accordingly (see supplementary file 1).

Reviewer 2

---Majors---

1. Comment: Current state of research

Answer: We thank you for this considerate remark and agree, that existing evidence should be clarified. Accordingly, we added information on effect-sizes of previous meta-analyses sorted by common mental disorders and clarified the previous research focus on stand-alone interventions (p.4):

'One of the first transdiagnostic reviews by Barak and colleagues[31] found small to large effect sizes of IMIs ranging from $d = 0.32$ (depression) to $d = 0.88$ (PTSD). Further reviews focused on IMIs as 'stand-alone' interventions, including meta-analytic evidence of efficacy in depression (SMD = 0.56, $n = 19$)[35], anxiety disorders (panic disorders: SMD = 0.83, $n = 6$) [36] or post-traumatic-stress disorder (SMD = 0.95, $n = 8$)[37]. However, IMIs in psychiatric disorders are less studied, albeit first RCTs show promising results [38].'

The manuscript addresses previous reviews in certain areas of health care (prevention of mental disorders, return-to-work in depressed patients). However, our comprehensive research could not identify a review on the topic of IMIs as aftercare focusing mental disorders, highlighting the importance of this review.

2. Comment: Technical aspects

Answer: We agree with your valuable remark on the importance of technical aspects of interventions under study. Accordingly, we differentiated the section 'data items' (p. 6) and added the discrete item 'technical characteristics (formerly under 'study design characteristics') with examples of dimensions to be studied ('e.g. Internet-/mobile-based, devices used, technical prerequisites'). Also, we replaced the term 'potential' with 'feasibility' in the section 'Conclusion' (p. 8) and in the section 'Strengths and limitations of this study' (p. 2,3). By doing so, we aim to evaluate feasibility, acceptability and reproducibility in the review and believe that implications of technical prerequisites and implementations are now sufficiently represented in the planned review. Again, we thank you for this comment as this will further improve the value of this review for clinical practitioners.

---Minors---

3a. Comment: Language of the intervention

Answer: We thank you for the important remark and included 'language' in the section 'data items' under 'setting' accordingly (p. 6).

3b. Comment: Patient or Clinician acceptability

Answer: We highly appreciate the reference to acceptability, a field we previously investigated in inpatients and clinicians (e.g. Hennemann, Beutel & Zwerenz, 2016). However, BMJ author guidelines for protocols do not provide a discussion section, where we certainly would have included these aspects. Nevertheless, with extending the data item 'technical characteristics' (see below, 3b), we specify the basis for discussing feasibility, acceptability and reproducibility as key aspects of implementation of IMIs in this review.

3b. Comment: Technical aspects

Answer: (see above, (3)). We agree with your valuable remark on the importance of technical aspects of interventions under study. Accordingly, we differentiated data items (p. 6) and added the discrete item 'technical characteristics' (formerly to find under 'study design characteristics') with examples of dimensions to be studied ('e.g. Internet-/mobile-based, devices used, technical prerequisites'). Thus, we aim to evaluate feasibility, acceptability and reproducibility in the review and believe that implications of technical prerequisites and implementations are sufficiently represented in the planned review.

3c. Comment: Therapeutic method

Answer: According to your valuable suggestion, we included 'psychological/therapeutic meth-ods' and 'synchronicity of contact' in the section 'data items' under 'intervention characteristics' (p. 6). Again, we thank you for this comment as this will further improve the value of this review for clinical practitioners.

Further corrections

---General---

We thank the manuscript reviewers for their considerate feedback and added an acknowledgement subsequently in the section 'contributorship statement' (p. 9).

---Abstract/Strength and Limitations---

1. To account for the prevalent heterogeneity in the field of IMIs and aftercare, we added a bullet point under 'Strengths and limitations of this study' subsequently (p. 2).

'Heterogeneity of studies in terms of clinical, methodological or statistical aspects will be considered carefully.'

2. We crossed out the second bullet point in the section 'Strengths and limitations of this study' and included information on search strategy in the first bullet point to increase conciseness of this section (p. 2).

'This review perform a sensitive search in electronic databases (...)'

---Objectives---

1. For further clarification of inclusion criteria regarding aftercare for patients with primary somatic conditions and comorbid mental symptoms/disorders, we crossed out the clause 'who received treatment for mental disorders' and rephrased into:

'(...) in maintaining treatment effects or in preventing symptom or disorder recurrence of mental disorders in adults.' (p. 4)

---Methods ---

1. We formally corrected information on minimum age of inclusion in section 'eligibility criteria' from '>18' to '≥ 18'. (p. 4)

2. For further clarification of inclusion criteria applying for patients, who received treatment for somatic conditions and aftercare includes comorbid mental symptoms/disorders (e.g. patients with chronic pain, cancer), we crossed out the clause 'or have been diagnosed with a mental disorder in somatic treatment' and replaced it with 'have received treatment for a mental disorder or a somatic condition' (p. 4, see above 'Objectives', comment (1)). We'd like to point out, that criteria for assessment and intervention objectives of mental symptoms/disorder are the same independent of preceding psychological or somatic treatment, as specified in the same section under (c) and the section 'Study design and interventions' under (g).

3. In the same section (p. 4), we added the temporal specification 'within the previous six months', to clarify focus on aftercare interventions following proximately to acute treatment.

4. To allow for active or inactive control groups that include internet-based information (e.g. links to health information) but not the comprehensive intervention under study, we crossed out the amendment '(...) where Internet or mobile applications are not the predominant methods' in the subsection 'Comparators' (p. 5).

5. In the section 'data items' (p. 6) we further differentiated the point 'study design characteristics' into:

'intervention characteristics (e.g. psychological/therapeutic methods, amount of human guidance, synchronicity of contact, duration of intervention), (d) technical characteristics (e.g. Internet-/mobile-based, devices used, technical prerequisites)'

Correspondingly, we specified this point in the abstract, subsection 'methods and analysis' (p.2). There, we crossed out the examples in brackets, as they are listed in detail in the section 'data items' (p. 6).

'Further data items to be extracted will be: Study design-, intervention- or technical characteristics, type of mental disorder or clinical symptom to be treated, target population items, setting, treatment engagement and assessment of additional outcome variables.'

6. In the same section, we added 'adoption of outpatient therapy' under (h) 'treatment engagement' to account for the importance of aftercare instruments in facilitating access to outpatient treatment (p. 6).

7. In the same section the examples 'amount of human guidance, assessments, duration of intervention' were transferred to the above mentioned point 'intervention characteristics' (p. 6).

---Conclusion---

1. In order to differentiate expected findings, we added a sentence on potential research cavities and the deduction of research strategies (p.8):

'In case of cavities in research areas or unsatisfactory confirmation, we will suggest future research strategies.'

---Search term---

1. To increase response rate, we included the terms 'text messaging' and 'Smartphone*' and corrected 'recurrence' into 'recurren*' (title/abstract, respectively).

---References---

As stated above, we added the following references to the manuscript and adapted the numbering consequently.

18 MacDonald, L., Chapman, S., Syrett, M., Bowskill, R., & Horne, R. (2016). Improving medication adherence in bipolar disorder: A systematic review and meta-analysis of 30 years of intervention trials. *Journal of affective disorders*, 194, 202-221. doi: 10.1016/j.jad.2016.01.002

19 Barkhof, E., Meijer, C. J., de Sonnevile, L. M., Linszen, D. H., & de Haan, L. (2012). Interventions to improve adherence to antipsychotic medication in patients with schizophrenia—a review of the past decade. *European Psychiatry*, 27(1), 9-18. 10.1016/j.eurpsy.2011.02.005

28 WHO. A health telematics policy. Report of the WHO Group Consultation on Health Telematics. World Health Organization (1998), Geneva

29 Ebert DD, van Daele T, Nordgreen T, et al. Internet and mobile-based psychological interventions: applications, efficacy and potential for improving mental health in Europe.: A report of the EFPA e-health taskforce. *Eur Psychol* under review.

33 Richards, D., & Richardson, T. (2012). Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clinical psychology review*, 32(4), 329-342.

34 Olthuis, J. V., Watt, M. C., Bailey, K., Hayden, J. A., & Stewart, S. H. (2015). Therapist-supported internet cognitive-behavioural therapy for anxiety disorders in adults. *BJPsych Advances*, 21(5), 290-290.

35 Kuester, A., Niemeyer, H., & Knaevelsrud, C. (2016). Internet-based interventions for posttraumatic stress: A meta-analysis of randomized controlled trials. *Clinical psychology review*, 43, 1-16.

36 Lauder, S., Chester, A., Castle, D., Dodd, S., Gliddon, E., Berk, L., ... & Berk, M. (2015). A randomized head to head trial of MoodSwings. net. au: an Internet based self-help program for bipolar disorder. *Journal of affective disorders*, 171, 13-21. doi: 10.1016/j.jad.2014.08.008

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Hennemann, S., Beutel, M. E., & Zwerenz, R. (2016). Drivers and Barriers to Acceptance of Web-Based Aftercare of Patients in Inpatient Routine Care: A Cross-Sectional Survey. *Journal of Medical Internet Research*, 18(12), e337.

MacDonald, L., Chapman, S., Syrett, M., Bowskill, R., & Horne, R. (2016). Improving medication adherence in bipolar disorder: A systematic review and meta-analysis of 30 years of intervention trials. *Journal of affective disorders*, 194, 202-221.

Nieuwenhuijsen K, Faber B, Verbeek JH, et al. Interventions to improve return to work in depressed people. *Cochrane Database Syst Rev* 2014(12):CD006237.

Richards, D., & Richardson, T. (2012). Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clinical psychology review*, 32(4), 329-342.

Olthuis, J. V., Watt, M. C., Bailey, K., Hayden, J. A., & Stewart, S. H. (2015). Therapist-supported internet cognitive-behavioural therapy for anxiety disorders in adults. *BJPsych Advances*, 21(5), 290-290.

Sander, L., Rausch, L., & Baumeister, H. (2016). Effectiveness of Internet-based interventions for the prevention of mental disorders: a systematic review and meta-analysis. *JMIR mental health*, 3(3).

VERSION 2 – REVIEW

REVIEWER	Vandad Sharifi Tehran University of Medical Sciences
REVIEW RETURNED	13-May-2017

GENERAL COMMENTS	The authors have addressed almost all the comments however they have added a clause that could be unclear or misleading that is including papers studying those who "have received treatment for a mental disorder OR a somatic condition within the previous six months" (see page 5 paragraph 1). Perhaps the latter is comorbid psychiatric and somatic conditions. Otherwise I have no further comments.
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REVIEWER	Berrouiguet, Sofian Brest Medical University Hospital at Bohars
REVIEW RETURNED	02-May-2017

GENERAL COMMENTS	Authors provided an outstanding revision of . Therefore, I suggest to accept this article for publication in BMJopen.
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VERSION 2 – AUTHOR RESPONSE

 Reviewer 1

1. Unclear specification of somatic condition in inclusion criteria (p. 4).
 Answer: We thank you for the considerate remark and agree with you on the ambiguous phrasing. We aim to also include studies of patients with primary somatic conditions (e.g. cancer, chronic pain) who receive an Internet- or mobile-based aftercare/follow-up post-discharge for comorbid mental symptoms (e.g. depression, anxiety). Thus, the preceding treatment may also be somatically oriented. However, we clarified the sentence according to your helpful comment and added "with comorbid mental symptoms":
 "who (b) have received treatment for a mental disorder or a somatic condition with comorbid mental symptoms within the previous six months."