Point-by-Point Response

Stakeholder Comments for Scoping Document

Health to technology assessment of antidepressant pharmacotherapies and cognitive behavioral therapies in treatment of major depressive disorder

commissioned by the Swiss Medical Board (SMB)

Assessment Team

Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich

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29 April 2020

Full name: Dr. Hanspeter Conrad

Job title: Spitaldirektor ipw, Präsident SMHC

Organisation: Swiss Mental Healthcare

Comment number	Chapter	Comment	Suggested change	Responses
General Comments				
1		Das Thema “Digital Psychiatry” ist noch fast nicht berücksichtigt. Vgl. dazu z.B. ein eigenes Schwerpunktkapitel “Part 5: Digital psychiatry – enhancing the future of mental health” im WPA-Lancet Zukunftsbericht von 2017 (Bhugra, D. u.a., The WPA-Lancet Psychiatry Commission on the Future of Psychiatry)	Aufzeigen des Nutzens von web-gestützten medikamentösen und psychotherapeutischen Hybrid-Behandlungsformen im Vergleich zu nicht web-basierten medikamentösen und psychotherapeutischen (oder kombiniert medikamentösen / psychotherapeutischen) Behandlungen	Many thanks for your comment and the material you suggested. We agree with you that digital CBT is an important topic. If possible, the effect of digital CBT alone or combined with traditional approaches will be explored in a subgroup analysis.

Full name: Drahomir Aujesky und Regula Capaul

Job title: Co-Präsidenten

Organisation: Schweizerische Gesellschaft für Allgemeine Innere Medizin (SGAIM)

Comment number	Chapter	Comment	Suggested change	Responses
General Comments				
1		Der Vorstand der Schweizerischen Gesellschaft für Allgemeine Innere Medizin (SGAIM) bedankt sich bestens für die freundlicherweise eingeräumte Möglichkeit einer Stellung-nahme im Zuge der Vernehmlassung. Der SGAIM ist es ein grosses Anliegen unnötige Behandlungen zu vermeiden, um eine optimale Behandlung für unsere Patienten sicherzustellen. Aus diesem Grund engagiert sich die SGAIM im Verein smarter medicine – Choosing Wisely Switzerland, um genau dieses Ziel proaktiv umzusetzen. Wir erachten die Fragestellung als wichtig und begrüssen daher die Durchführung eines entsprechend HTAs.		Thank you for your comment.

Full name: Susanne Walitza
Job title: Prof. Dr. med.
Organisation: SGKJPP – Schweizerische Fachgesellschaft für Kinder- und Jugendpsychiatrie und -psychotherapie

Comment number	Chapter	Comment	Suggested change	Responses
General Comments				
1		General Comments: The topic is of high interest because there is since many years and also currently a controversial public discussion in Switzerland, weather AD are adequately prescribed and regarding evidence based findings of outcome, side effects and benefits for patients. The study is planned like a review or as the authors described as a network-meta-analysis. The design is also very similar to the development of S2 Guidelines (evidence based guidelines) according to AWMF. The German Guidelines S3 will be revised at the moment. We recommend to avoid to do everything double and cooperate with the AWMF working group for depression. Furthermore the authors of the proposal should have a look if there is a meta-network analysis under way. The most important comment from the SGKJPP is to take children and adolescents also into account of the planned analysis. Around one in ten adolescents worldwide and in CH will develop clinically relevant depression until they reach the age of majority. About half of those affected have at least one relapse, a third of the diseases are chronic. In adolescence, depression is already the disease that is responsible for most of the years of life lost (DALYs).		Many thanks for your comments and suggestions. We do agree that depression in children and adolescents is a highly relevant topic; however, we consider children and adolescents to be a special population (e.g. in relation to heterogeneity of AD mechanisms and differences in causes of depression) that needs to be addressed separately. An examination of the effectiveness of antidepressants in this population is currently out of scope for this HTA. As for comorbidity, we agree that it is important and frequently encountered in patients with depression. We will explore it to the extent possible depending on available information in the studies.

		For children and adolescents psychotherapy is the first-choice treatment, in cases of severe, recurrent or treatment resistant illness courses of depression, additional pharmacological therapies are usually recommended. In Switzerland however, no antidepressant drug is licensed for minors. One of the reasons is that a rise in suicidal ideations (but not completed suicides) has been reported in youth and young adults in the first weeks of antidepressant treatment when comparing antidepressant drugs with placebo .Therefore a multicenter study (Basel Zurich and 6 other centers in Switzerland), are currently undertaking a large-scale clinical trial, the Omega-3-pMDD trial, funded primarily by the Swiss National foundation (SNF ID33IC30_166826) to assess the antidepressant efficacy ofomega-3 fatty acids supplementation in pediatric depression (www.omega3.uzh.ch). We recommend also to take further interventions into account. Other Points: Comorbidity is the rule and not the exception. Guidelines and studies do very often avoid to investigate this in regard of complexity of the studies. But this would be a point with which the studies could go beyond previous reviews and guidelines.		

Full name: Markus Gnaegi
Job title: Ressortleiter HTA und Amtstarife
Organisation: santésuisse**:**

Comment number	Chapter	Comment	Suggested change	Responses
General Comments				
1	Gesamteindruck	Das Scoping ist gut aufgebaut, adressiert die relevanten Fragestellungen mit der notwendigen Tiefe. Im Gegenzug wird weder aufgezeigt, in welchen Datensammlungen die Suche erfolgte noch mit welchen Suchkriterien diese gemacht wurde. Es ist somit nicht abschätzbar, welche effektiven Evidenzen mit einem ausführlichen HTA erwartet werden dürfen.		Thank you for the comment.. We have included details on the planned search strategy that will be conducted in the Medline, Embase, Cochrane and PsycInfo databases, in the revised scoping document.
2	Summary	Die Zusammenfassung der wichtigsten Punkte der Literatursuche ist sehr hilfreich. Die aktuelle Qualität der Evidenz wird aufgezeigt. Entsprechende relevante Lücken können so adressiert werden.		Thank you for your comments.
3	1	Die Wirkung von Antidepressiva der zwei Wirkstoffklassen soll möglichst breit auch mit Verhaltenstherapie vor allem auf die lange Frist untersucht werden. Unterstützt wird die Berücksichtigung einer Schaden-Nutzen-Betrachtung explizit.		
4	3	Die PICO-Fragen werden nachvollziehbar beantwortet. Die vorgeschlagene Subgruppenanalyse wird unterstützt. Die Berücksichtigung von QALY bei der ökonomischen		

		Beurteilung der Intervention ist zielführend.		
Specific Comments				
	Objectives	Auch wenn grundsätzlich die Frage des Einsatzes von Antidepressiva in der Mittel- bis Langanwendung interessant ist (Wirksamkeit und Kosten), ist nicht nachvollziehbar, warum Studien mit Einsatz von Antidepressiva <12 Wochen per se ausgeschlossen werden. Damit und im Vergleich sind wichtige Erkenntnisse möglich, die Einfluss auf die Kosten – Nutzenfrage haben können. Dies auch bei der Patientenpopulation, die angesprochen ist (Patienten mit einer initialen MDD).	Kein Ausschluss von Studien, welche AD-Einsatz von <12 Wochen ausweisen; eine anschliessende Abgrenzung ist zu prüfen.	Extensive literature reviews and meta-analyses have already been performed to assess the effectiveness of antidepressants in the acute phase (up to 12 weeks) (e.g. Cipriani et al. 2018 Lancet). However, in practice antidepressants are usually continued for several months after initial remission as continuation or maintenance therapy to prevent relapse. The effectiveness and safety of antidepressants beyond the acute phase remains unclear with RCTs and observational studies showing conflicting results. As the planned HTA aims to fill this gap regarding the mid-to-long term outcomes as well the benefit-harm balance of MDD treatments, we chose to include studies that have a follow-up of more than 12 weeks. However, we will classify the included studies according to duration of treatment and a subgroup analysis will explore the effect of duration of treatment on outcomes (i.e. < 12 weeks, 12 weeks-6 months, 6 months-12 months, 12 -24 months and >24 months).
	iii. Comparator – Subgroupes	Die nähere Betrachtung von Subgruppen ist im Bereich der Antidepressiva sehr wichtig. Dazu gehören insbesondere die Untergruppen „Stärke der Depressionen“ oder auch „Alter“. Zusätzlich wünschenswert ist die Unterteilung nach „Klassen der AD“. Dies insbesondere auch in Bezug auf Verträglichkeit (in der Langzeitanwendung).	Zusätzliche Subgruppen: AD-Klassen	We agree with you. Depending on the available information, we will investigate differences between various subgroups, including AD drug classes, CBT types and delivery formats, severity of depression, age etc.

Full name: Markus Wolf / Birgit Watzke
Job title: Oberassistent / Senior Researcher
Organisation: University of Zurich, Department of Psychology, Clinical Psychology and Psychotherapy Research

Comment number	Chapter	Comment	Suggested change	Responses
General Comments				
#1	1	Overall, I found the intro very well written. However, it appeared quite short and parts of it read incomplete which I assume was intended to keep it short but I think it does not represent the full picture and bears the risk of oversimplification. For instance, depression classification is not based on severity only. In the same vein, environmental factors are not limited to “early trauma”. According to the guidelines, management of MDD – in particular first episodes with full remission or recovery - does not always have to follow the three phases, but rather, “maintenance treatment” is recommended for certain subgroups, mostly high risk patients, i.e. those with previous episodes (see classification) or residual symptoms. A more precise classification should be presented and linked with more specific treatment recommendations rather than stating that AD or SSRI “are the first-line treatments in depression” which falls	Even if they are not subject of this review, it might be considered to initially present the full range of (unipolar) depression, incl. recurrent, chronic, persistent affective disorder based on classification systems such as DSM/ICD, i.e., beyond a pure mild, moderate, severe classification based on HAMD etc, because there are specific assumptions about etiologies and illness mechanisms that affect treatment recommendations for the various forms/ courses. We also recommend to be aware of the pitfalls when using the HAMD for the definition of severity level (cp. Kriston & Wolff, 2017). Maybe refer to the German S3-Guideline for unipolar depression –in addition to APA and EPA guidelines--which does not recommend AD as first line treatment for all forms of depression but rather AD OR psychotherapy (mild, moderate depression), and AD AND PT (severe depression/). Guidelines vary in their methodical quality (and neutrality). Therefor we recommend to refer to guidelines with high methodical standards including systematic literature	Many thanks for your comments and suggestions. The document you reviewed was a scoping document aiming to define and establish an appropriate research question. The revised version includes additional details. However, a full picture of this very complex topic is beyond the scope of this document. The issues you’ve mentioned will be comprehensively discussed in the assessment report. As you pointed out, we will contextualize the final results for the Swiss setting, taking into account the availability of treatments, the health care system, and the costs. Regarding the efficacy and effectiveness of treatments, we will consider both and will largely depend on the available literature.

		short of the complexity of unipolar depression. A guideline that differentiates between various forms is the German S3-Guidline for unipolar depression. One additional - crucial - factor for initial treatment decision is availability of treatment within the care system (besides the other factors you are mentioning in the introduction). It reads that “multiple forms of psychotherapy have been examined with no superior…”, which is a bit of an oversimplification. Is it planned to consider both “effectiveness” and “efficacy”?	reviews, systematic consensus procedures and, especially, representative expert consortium (vs. guidelines by single professional associations with potential conflict of interest). Please be aware of availability of treatments as important issue referring to a barrier or an enabler when it comes to implementing recommendations for treatment choices within the Swiss health care system. Be more precise about the forms of psychotherapy for which evidence is available and/or that are recommended by guidelines. We recommend to take into account the different conceptions of “effectiveness” and “efficacy” and to decide which aspects (or both) should be considered.	
#2	1	It might appear nit-picky, but in some instances the language used to describe literature findings reads suggestive. For instance paragraph on Harms: “…a high frequency of harmful events…”; “antidepressants are indeed associated with a greater risk…,”; Para on Patient preference: “…people generally preferred psychotherapy…”	In the intro, I suggest to use a more neutral language and to report results as exact numbers/proportions rather than in a narrative way, if possible.	It was not our intention to sound biased or draw any conclusion on the effectiveness of antidepressants. The background information has been revised.
#3	3	Will unpublished data be considered? If so, how will it be handled?	Include a para about if and how unpublished data will be handled or considered.	Both published and unpublished data will be included. A detailed search strategy has been added to the revised scoping document.
Specific Comments				
#4	3 i	How is “treatment resistant” defined? Why are recurrent and also chronic depression excluded from the analyses?	Include a brief definition of treatment resistance	The revised scoping document has been amended to include a definition of treatment-resistant depression, i.e. episodes of major depressive disorder that do not respond to

				two consecutive treatments with antidepressants, used for a sufficient length of time at adequate dosages. Treatment-resistant and chronic depression will be excluded as they constitute a category of “persistent” or difficult-to-treat depression that is distinct from major depressive disorder (EPA, DSM-5). For such types of patients, the standard treatments are often not sufficient or not effective. Therefore, including such cases in the HTA might lead to an underestimation of the efficacy/effectiveness. In cases of mixed participation in the trials, we will include trials that included no more than 10% treatment-resistant depression cases and conduct further sensitivity analyses to assess the impact of including such trials in the overall analysis.
#5	3 ii	If guided and unguided self-help or distance interventions (internet, telephone) are included and counted into CBT, this should be accounted for in moderator analyses because there is not enough evidence that these forms are as efficacious and effective as bone-fide CBT and this could bias the results.	Include types of CBT and modes of delivery (group, individual) as subgroup or moderator variable.	We agree the effect estimates could be affected by moderator factors other than the treatment indicators and adjusted confounders. We will examine the study-level and meta-analysis quality of evidence within the GRADE domains. When the evidence is deemed affected by moderators, any differences in effect estimates in different types and delivery formats of CBTs will be examined through subgroup analyses using meta-regression (due to likely violation of randomization at subgroup level) and using leave-one-out sensitivity analyses.
#6	3 ii	For CBT the “3rd wave” is a relevant development.	It is recommended to include studies on CBT incorporating the “3rd wave” in addition to traditional CBT.	We agree that different types of CBT might have different effects in reducing depression symptoms and newer (e.g. third-wave) therapies might be more effective than

		The definition of CBT as presented in the text would also fit to other psychotherapeutic approaches. (Maybe this is an artefact as the citation is not displayed in the original context anymore.)	Please be more specific in the (formal) definition of CBT.	traditional CBT. This HTA will include both traditional and “third-wave” CBTs and we will examine whether there are differential effects between these types. The definition of CBT (including types and delivery formats) has been amended.
#7	3 iii	Age is dichotomized into two categories which does not allow to explore (non)linear trends, or to describe how treatments work in the age spectrum where they are prescribed most.	Use age as continuous variable or >2 categories.	This HTA will likely include only study-level aggregated data as it is improbable that we will be able to access individual patient data despite requests. It will therefore be difficult to meaningfully include age as a continuous variable. Furthermore, we do not expect significant linear age effects as supported by previous literature. However, depending on the reporting of individual studies, we will aim at having more than two categories for age.
	3 iii		According to treatment recommendation and diagnostic systems (ICD) it would make sense to categorise severity into three groups (mild, moderate, severe). Otherwise there will be a risk for ambiguity for the group of patients with moderate depression (for which distinctions seems to be crucial).	We agree and definitely aim for classifying the severity of depression as mild, moderate and severe. We have clarified this point in the document.
#8	3 iii	Ad subgroup analyses: Add study quality, allegiance, and other important potential sources of bias. One important outcome of this HTA could be to systematically assess the quality of the current evidence in the various domains.	Add in the Methods a paragraph about planned risk of bias assessment. Add a section that refers to relevant risk of bias variables such as overall risk of bias, allegiance, adherence, recruitment source, year of publication, and other important aspects known to be associated with effects. Also consider to add mode of outcome assessment as a subgroup, i.e. self-report (e.g., PHQ-9) versus clinical expert evaluation (e.g. HAMD).	As we have already mentioned, the document you have received was for the purpose of defining research questions. In the revised document we have included all the necessary descriptions and explanations, including a detailed description of PICO, search strategy, analytical methods, assessment of bias and quality of evidence, etc.

#9	3 iii		Mode and source of patient recruitment (by advertisements, by recruiting in clinical setting, etc.) might be a proxy for estimating external validity or representativeness of samples.	
#10	3 iii		It is recommended to include also comorbidity (referring to other mental disorders) as variable. Comorbidity in depression is high in real-world patients.	We agree that in clinical practice patients with depression often have comorbid mental health disorders. Comorbidity is not considered an exclusion criterion and will be explored to the extent possible considering the availability of information in the studies.
#11	3 iv	Because depression is a disorder that affects the whole individual, families and relationships, and functioning in various domains, it will advance the field to learn in this HTA about effects beyond usual endpoints (i.e. symptoms). QoL and functional capacity are already mentioned but there might be other domains that are increasingly discussed in the literature as important endpoints in mental health research, such as recovery, well-being, social functioning, or social validity. It would be good to see how these are recognized in the current literature.	Maybe include endpoints that go beyond symptom status, and that help to estimate the decrease of illness burdens as a consequence of treatment.	We will consider all outcomes now listed in our PICO, including the patient-important outcomes that you mentioned. However, we anticipate that not all clinical and patient-important outcomes will be available in the included studies.
#12			Maybe it is worth the effort to include the distinction between intervention drop outs and assessment drop outs into the analyses.	While this is highly interesting, it cannot be addressed within the scope of this HTA.

Full name: Andreas Daurù
Job title: Leiter Recovery und Sozialpolitik
Organisation: Stiftung Pro Mente Sana

Comment number	Chapter	Comment	Suggested change	Responses
General Comments				
1	2. Objectives	Wir erachten die Wahl der Zielsetzung des Projekts als sinnvoll		Thank you for your comments.
	3. iv Outcomes II. Safety or harm outcomes	Hier sind wir der Ansicht, dass die Akzeptabilität nicht nur im Bezug auf die Nebenwirkungen untersucht wird, sondern auch aus Sicht der zu behandelnden Person. Inwieweit ist die behandelte Person in die Wahl der Medikation einbezogen worden? Bzw. wie wirkt sich die Mitsprache bei der Wahl der Therapieform (CBT oder AD) auf die Akzeptabilität eines allfälligen Medikamentes (AD) aus (Frage der Adherence).		We agree with you that patient preferences are extremely relevant. As such, we have proposed a quantitative benefit harm assessment as part of the HTA to incorporate the patient treatment goals and values. In such an analysis, we will consider all efficacy and safety outcomes and convert them into a common scale using patient preferences (i.e., relative importance of the outcomes) and evaluate whether ADs and/or CBT provide an overall net benefit compared to their comparators.

Full name: Prof. Dr. Erich Seifritz/Dr. Pierre Vallon
Job title: Psychiatrists and Psychotherapists
Organisation: SGPP – Schweizerische Gesellschaft für Psychiatrie und Psychotherapie

Comment number	Chapter	Comment	Suggested change	Responses
General Comments				
Page 1, 6 and 11		Harms of ADM (antidepressant medication) are mentioned. What are the harms of ADM? Recent sensitivity analysis shows no health risk of antidepressants if the health risk of the underlying disorder (depression) is substracted from the risk of depressed patients treated with ADM (Dragioti E, Solmi M, Favaro A, Fusar-Poli P, Dazzan P, Thompson T, Stubbs B, Firth J, Fornaro M, Tsartsalis D, Carvalho AF, Vieta E, McGuire P, Young AH, Shin JI, Correll CU, Evangelou E. Association of antidepressant use with adverse health outcomes: a systematic umbrella review. JAMA Psychiatry. 2019. (doi:10.1001/jamapsychiatry.2019.2859)) It is unclear how "harm" is defined in this context. Is a short term side-effect considered as harmful? How do you disentangle drug-induced harm rather than disease-related symptoms? How do you plan to account for harm or side-effects that are associated with the study protocol per se? For example, most studies use fixed dose designs, which is in so far disadvantageous as the treatment under study cannot be adapted to the individual's side-effects.	This would be a valuable topic for further study, since many questions are not elucidated so far.	Thank you for your comments, suggestions and additional literature. We agree that it is hard to separate the side effects of treatments from other drug/study-related/individual factors. This issue is more pronounced in dealing with uncontrolled data, such as observational studies. The uncertainty that remains in the literature regarding the possible harms (or lack of harms) of MDD treatment makes it extremely essential for us to identify and assess these harms, apart from the expected treatment benefits. In methodologically well designed and conducted RCTs we expect that the treatment arms will be approximately comparable. Since not all RCTs are of high quality, the presence of residual confounders, effect modifiers or mediators that may influence the treatment effects can't be excluded a priori. To the extent possible, we will take into account such problems by performing subgroup and sensitivity analyses. As you mention, the conditions in which trials are conducted may not be close to the true clinical reality. Therefore, as much as

		Clinical reality is completely different, if the psychopathological or physical state of the is not satisfying during treatment, the therapy is adapted. This is not possible in RCTs, and particularly even less possible in fixed-dose designs. It is also not clear whether reported harm including osteoporosis etc. reflects risk of disorder vs treatment, or whether it reflects risk of the interaction of age and disorder vs treatment?		possible, alongside RCTs we will also include evidence from observational studies which are generally more reflective of the real-world.
Page 1 and 11	2	Authors claim that adverse events are underreported. What is the evidence of this statement? RCTs for the registration of a drug are strongly regulated, and the study design are transparently provided to the public, e.g. on clinicaltrial.gov.	Adverse effects of psychotherapy are clearly underreported. The reporting style or bias of adverse events should be compared between studies on ADM and psychotherapy efficacy (Locher C, Koechlin H, Gaab J, Gerger H. The other side of the coin: nocebo effects and psychotherapy. Front Psychiatry. 2019;10:555. (doi:10.3389/fpsyt.2019.00555); Lilienfeld SO. Psychological treatments that cause harm. Perspect Psychol Sci. 2008;2(1):53–70. (doi:doi: 10.1111/j.1745-6916.2007.00029.x). This is a clearly open question that has not been systematically adressed yet. Authors claim that adverse events in ADM RCTs are underreported. No convincing evidence exists for this claim. This could be an interesting hypothesis to be formally tested here.	We agree. It is unclear if/how AE reports may be biased or not (and if yes, in which direction), and we cannot simply assume an underestimation. We reformulated the text by removing this assumption. We agree that testing this hypothesis would we very interesting. However, this will not be the aim of the present project. We will mention this issue in the discussion/limitations of this HTA.
Page 11	3	Alleged prolonged sexual side effects of ADM	No systematic evidence of prolonged sexual side effects after withdrawal of SSRI, as reported by observational case descriptions. The EMA's Class Recommendation is purely based on observational reports. EMA is forced to publish this, even the evidence and the	No allegations were made regarding sexual dysfunction after withdrawal of SSRIs. We described the possible side effects of long-term use of antidepressants as they have been reported in the literature (references included with two meta-analysis one of which includes 58 RCTs). We agree that conclusions in the

			source of the evidence is completely unclear. This might be an interesting topic for a systematic review.	literature regarding many of the reported side effects have been drawn from observational studies rather than RCTs. While RCTs represent the highest level of evidence, observational studies, if conducted properly, can significantly contribute to filling gaps particularly regarding long-term safety data.
Page 1 and 10	4	Authors claim that it is clear that mild depression does not respond to ADM. However, a recent study has shown that ADM has similar efficacy on depression in all severity levels, that is mild, moderate and severe depression, if the depression core symptoms are considered as target symptoms. In fact, the 17-item HDRS measured both core and non-core depression symptoms (Hieronymus F, Lisinski A, Nilsson S, Eriksson E. Influence of baseline severity on the effects of SSRIs in depression: an item-based, patient-level post-hoc analysis. The Lancet Psychiatry. 2019;6:745-752. (doi:10.1016/S2215-0366(19)30216-0)). In addition: There is a bias of HRDS as instrument to quantify severity of depression, since main effects of depression and side effects of medication overlap and obscure effects of treatment on depressive core symptoms (Hieronymus F, Lisinski A, Nilsson S, Eriksson E. Influence of baseline severity on the effects of SSRIs in depression: an item-based, patient-level post-hoc analysis. The Lancet Psychiatry. 2019;6:745-752. (doi:10.1016/S2215-0366(19)30216-0)	The Hieronymus et al 2019 study raises an interesting new lead to understanding the bias of HDRS as outcome measure. It would be an interesting and important question to address this issue more systematically here.	We refer you to the following phrases from the document: *"Differences in the effectiveness of antidepressants as a function of severity of depression is controversial. A few individual participant data (IPD) meta-analyses have examined the influence of baseline severity on the efficacy of antidepressants with contradicting results. While two IPD meta-analyses found that the superiority of antidepressants increases with baseline severity, others found no influence"* (references were included). No claims were made regarding the efficacy of antidepressants in mild depression throughout the document. As patient-level data will most likely not be available, we will rely on aggregate data of response rates as defined by study investigators (most of whom have used HAM-D scale). When assessing how treatment effects differ by depression severity level, the limitations and pitfalls of using such scales will be kept in mind and discussed.

Page 1 and xx	5	It is commonly accepted that the combination of CBT and ADM are more efficacious than each treatment form alone (Cuijpers P, Noma H, Karyotaki E, Vinkers CH, Cipriani A, Furukawa TA. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry. 2020;19(1):92-107. (doi:10.1002/wps.20701)). However, is this really true? All treatments in medicine and psychiatry contain a certain amount of placebo effect. In RCT of AMD, the placebo effect is subtracted from the total effect in the drug patient group, while the effect of treatment in psychotherapy researchs cannot be disentangled from the placebo effect (Benedetti F. Placebo and the new physiology of the doctor-patient relationship. Physiol Rev. 2013;93(3):1207-1246. (doi:10.1152/physrev.00043.2012)). In addition, the specific effects of psychotherapy are not understood and cannot be separated from generic effects of doctor-patient relationship, expectation effects etc (Furukawa TA, Noma H, Caldwell DM, Honyashiki M, Shinohara K, Imai H, Chen P, Hunot V, Churchill R. Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. Acta Psychiatr Scand. 2014;130(3):181-192. (doi:10.1111/acps.12275); Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Hollon SD. Component studies of psychological treatments of adult depression: a systematic review and meta-analysis. Psychother Res. 2019;29(1):15-29.	This would be probably the most important research question that could be here addressed.	In comments 5-7, you raised very important points about the effects and components of placebos in different intervention contexts. As suggested, the mechanism of placebos in CBT interventions is not yet clear. These are open questions that should be investigated separately. The potential effects of placebo will be discussed in the full assessment.

		(doi:10.1080/10503307.2017.1395922); Cuijpers P, Karyotaki E, Reijnders M, Ebert DD. Was Eysenck right after all? A reassessment of the effects of psychotherapy for adult depression. Epidemiol Psychiatr Sci. 2019;28(1):21-30. (doi:10.1017/S2045796018000057); Cuijpers P, Reijnders M, Huibers MJH. The role of common factors in psychotherapy outcomes. Annu Rev Clin Psychol. 2019;15:207-231. (doi:10.1146/annurev-clinpsy-050718-095424)		
Page 5	6	Since no placebo control in psychotherapy research exists, the true efficacy compared to drug treatment cannot be assessed truly Recent research shows an extremely strong placebo effect of psychotherapy (Gaab J, Kossowsky J, Ehlert U, Locher C. Effects and components of placebos with a psychological treatment rationale - three randomized-controlled studies. Sci Rep. 2019;9(1):1421-1428. (doi:10.1038/s41598-018-37945-1))	This could be systematically compared to the effect of ADM studied here.	
Page 5	7	The definition of mild, moderate and severe depression according to ICD and DSM does not necessarily correspond to the severity of the disorder measured using HDRS, severity in DSM/ICD is a categorical (number of symptoms) and HDRS is a dimensional (severity of symptoms) measure. Therefore, study samples in RCTs have a usually mild to moderate severity, compared to real patients.	This is also an open question in current research and might be addressed here. An interesting new lead is the finding that in RCTs the variability of ADM vs response is higher than the variability of placebo response. This suggests that there might be clinical subtypes of ADM response, while the placebo response seems to be more generic (Maslej MM, Furukawa TA, Cipriani A, Andrews PW, Mulsant BH. Individual differences in response to antidepressants: A meta-analysis of placebo-controlled randomized	

			clinical trials. *JAMA Psychiatry.* 2020. (doi:10.1001/jamapsychiatry.2019.4815). It would be interesting whether psychotherapy response variability is more like the variability of ADM or of placebo.	
Page 8	8	Authors cite the Haller al "Helsana" study finding an 8.7% prevalence rate of at least one ADM prescription within 12 months.	It would be interesting to learn the medical indications that led to this prescription rate. Were this patients with depression, or were these patients treated for other than depression conditions, such as pain, sleep problems etc.? Among the Helsana insured persons, 17% received an ADM prescription of their general practitioner and only 3% from their psychiatrist. This could indicate that psychiatrist have more time to discuss with patients and clarify the indication to an antidepressant treatment.	Further exploration of the prescription patterns of antidepressants would be indeed very interesting. However, that is not within the scope of this HTA.
Page 10	9	The long term effects of ADM is questioned.	It would be highly relevant to better understand long term effects of treatment for depression. Here, a review of the comparative evidence of psychotherapy and ADM efficacy would be interesting and novel.	We agree. The purpose of the scoping process was to explore the literature and identify research gaps, one of which was found to be related to the long-term effects of the treatment of MDD.
Page 10	10	Authors claim that it is unlikely that the efficacy and safety of ADS differ by populations and that it may thus be important to study the differences in the effects of CBTs for different regions	Why is this likely? The expectation effect is strong both for the efficacy of ADM and of psychotherapy. And this varies strongly by region. Most important is the differential efficacy of the formats by which psychotherapy is delivered. It has clearly been shown in meta-analyses that it was impossible to demonstrate higher efficacy of face to face CBT compared to group, self-help and unguided internet based CBT (Karyotaki E, Ebert DD, Donkin L, et al. Do guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data	Thank you for pointing that out; the sentence has been rephrased to reflect the possible differences of both AD and CBT in different populations and regions. The differential efficacy of different CBT delivery formats is certainly of interest and we will explore it in subgroup analyses.

			meta-analysis. Clin Psychol Rev. 2018;63:80-92. (doi:10.1016/j.cpr.2018.06.007); Karyotaki E, Riper H, Twisk J, et al. Efficacy of Self-guided Internet-Based Cognitive Behavioral Therapy in the Treatment of Depressive Symptoms: A Meta-analysis of Individual Participant Data. JAMA Psychiatry. 2017;74(4):351-359. (doi:10.1001/jamapsychiatry.2017.0044); Cuijpers P, Noma H, Karyotaki E, Cipriani A, Furukawa TA. Effectiveness and acceptability of cognitive behavior therapy delivery formats in adults with depression: a network meta-analysis. JAMA Psychiatry. 2019;76(7):700-707. (doi:10.1001/jamapsychiatry.2019.0268). Would be an important new topic for a review.	
Page 11	Health economics 11	No comparison studies of full health economic costs evoked by depression treated with psychotherapy vs ADM exist. Economic costs ADM should be related to those of psychotherapy, and the cost effectiveness of different psychotherapy delivery formats (face to face, group, internet based self help like e.g. deprexis etc) should be compared. Most important are the indirect disease costs, rather than the direct costs.	This would be extremely interesting, especially for the situation in Switzerland. An important question is also how innovative new psychotherapy delivery formats (internet based, self help digital devices etc.) could be used to save costs and increase the availability of psychotherapy without cost increase.	We agree that the exploration of the economic costs of AD and CBT are extremely interesting. The type of economic analysis and the extent to which we can compare AD and different formats of CBT taking into account both a health and societal perspective relies on the availability of published data and publicly available Swiss data sources.
Page 11	Methods 12	The methods described here should be reconsidered, they are based on groups and studies, more advanced metanalytic methods include single case (patient-level) comparisons rather than these study- or group level meta-analyses.	Please clarify which exact methods and why will be employed. This depends on the specific hypotheses of the study, which should be clearly stated.	We agree that meta-analysis based on individual patient data would be preferable. However, given that we are unlikely to gain access to all individual patient level data, we will primarily be focusing on study-level data. Adequate methods to reduce potential biases and account for differences in populations/treatments will be applied.

				Additional details on the methodological approaches have been added to the amended scoping document. Fully detailed methodological approaches will be presented in the protocol that is currently being prepared.
Page 11	General comment 13	It is not clear what purpose of this work is meant for. Abundant meta-analytic studies were already published about this issue, on a high quality level. One should attend of the authors a clear statement, based on a serious literature review, regarding the aim of their research and the hypothesis they want to discuss.	This is the most important issue that should be clarified before work is initiated. No hypothesis – no chance for useful results! Please provide clear hypothesis statements and the corresponding appropriate methodological approaches to address them.	The main purpose of the scoping document you have received was to explore the current literature to frame a research question and PICO criteria. We acknowledge there has been already extensive work done to examine the effectiveness of antidepressants. However, most of the assessments have been done during the acute phase of treatment and significant uncertainty lies beyond that phase. As we clearly mention in the objectives of the scoping document, we will focus on the use of antidepressants and/or CBT beyond the acute phase of management while taking into consideration both the benefits and harms of each. As antidepressants are often taken for a long period of time that extends beyond the acute phase as recommended by national and international guidelines, an extensive analysis of the available evidence from a mid- to long-term perspective is needed. It is also noteworthy that none of the existing systematic reviews/meta-analyses carried out a benefit-harm assessment of the MDD interventions. It may be hard to draw any conclusions regarding the overall benefit of an intervention/treatment if the treatment outcomes regarding efficacy and safety are assessed separately. Therefore, in this HTA, we will evaluate the benefit-harm relationship of the interventions, taking into account all treatment outcomes (positive and negative) simultaneously on

				a common scale, and assess the benefit-harm balance (i.e. whether benefits outweigh the harms or vice versa).

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Comment number	Chapter	Comment	Suggested change	Responses
General Comments				
	Chapter 1, paragraph "antidepressants"	Not clear what kind of classes of antidepressants are going to be included in the analysis. Some antidepressant mentioned in table 1 of the scope do not exist in Switzerland, others are missing; what about phytotherapy (or other non-pharmacological treatments)?	Clear definition of what classes are going to be included or excluded as well as mentioning of specific substances included in the final analysis.	Many thanks for your comments and suggestions. The methods section in the revised scoping document has been amended to include the specific antidepressants/classes of antidepressants as well as the different types and formats of CBT that will be included in the analysis.
	Chapter 1, paragraph "antidepressants"	There are some meta-analysis showing clear efficacy in mild-moderate MDD (Stewart et al. J Clin Psychiatry 2012, NNT 3 to 8) and some analysis showing that antidepressants are effective independent of initial severity of major depression (Furukawa et al., Acta Psychiat Scand. 2018) -> Furukawa et al. is a paper that is cited in the document, though not really discussed in depth.	These facts need to be discussed in more detail in the scope as well as included.	We agree that, as part of our scoping process, we identified a wide range of differences in reported efficacy and safety across studies and between different levels of depression severity. One of the most uncertain area is the effectiveness of antidepressants and/or CBT across different levels of MDD severity. The in-depth analysis of these effects cannot be included in the scoping documents. A detailed discussion and any possible conclusions regarding the differential effect of either treatment by MDD

				severity can be expected from the full HTA report.
	All document	The methodology for this HTA project is not described in detail.	It is recommended to use internationally accepted methodology allowing a fair comparison between all substances and non-pharmacologic therapies. This analysis should follow international standards and reflect the different study designs, dates of studies (some substances are very old and it is known that placebo effect has increased significantly over the years and decades), double blind randomized trials vs other designs etc..	Please note that the content of the document you received was for the purpose of scoping, i.e. to establish research questions and PICO for the HTA. Further details on methods and analyses have been added to the amended document. A fully detailed protocol will be prepared and registered on PROSERO after the approval of the scoping document by the SMB.
	All document	The scoping document gives the impression that the authors are assuming that antidepressants are not effective per se even if studies cited in the document show effectiveness. It seems that there is an unbalanced appreciation of the existing evidence towards a general scepticism of effectiveness of pharmacological therapies for depression. Pharmacotherapy has been shown to be very effective and lifesaving and the proposed objectives might perhaps only lead to more confusion rather than clarification. Efficacy of psychotherapy for instance is very controversially discussed in literature and has generated much less evidence-based data compared to psychopharmacology.	- Balanced appreciation of pharmacotherapy - Psychotherapy should also be more critically reflected	Appearing unbalanced or biased in this document was not intended. We do not aim to draw any conclusions on the effectiveness of either antidepressants or psychotherapies but rather to provide an overview of the current evidence to frame the research question and the PICO. We have now revised the explanations in a neutral way.

	All document	Depression is a very heterogeneous disease that needs a very individualized treatment	Scoping document should include heterogeneity of depression as a relevant subject having an impact also on effectiveness of treatments	We agree that MDD is a highly heterogenous disease and two patients with MDD may not share the same symptoms or experience the same effect of drug treatment or CBT. The indication for intervention types and doses as well as the treatment results would also obviously differ. In the subgroup analyses, we will characterize the study participants based on their baseline health conditions and in particular the severity of depression.
	Chapter 1, introduction	Swiss guidelines are not mentioned in the scope	It is recommended to include the Swiss guidelines amongst other international guidelines as this HTA should reflect the Swiss perspective on the use of antidepressants (SGPP 2016)	We agree. As we aim to draw conclusions for Switzerland, we are now referencing the Swiss guidelines on treatment of MDD in the revised document.
	Chapter 1, paragraph “cost effectiveness of depression treatment”	The perspective of this assessment should be from a Swiss perspective. It is thus not helpful to discuss cost-effectiveness data from the US	Relevant Swiss data only should be included	A detailed health economic assessment plan has been included in the revised scoping document. The planned economic assessment will consist of a review of the published economic literature (national and international), cost-effectiveness considerations based as much as possible on Swiss data, and a budget impact analysis. The extent of transferability of results from international studies will be thoroughly examined and costs will be adapted to ensure comparability of international studies to the Swiss context. If sensible given the available materials, a de novo cost-effectiveness analysis will be performed. With regards to the clinical effectiveness, we do not expect any relevant differences in the efficacy and safety of AD drugs regardless of

				where the RCTs are performed. However, as we noted in the document, there may be differences in efficacy/safety, particularly of CBTs, due to mode of administration or culture. We will try to examine the individual studies assessing CBTs to see if the effect is applicable to the Swiss context.
Specific Comments				
	Chapter 1, introduction	Increase in prescription of antidepressants over time is not only due to depression, but also due to other psychiatric conditions (anxiety disorders, PTSD, and many other psychiatric disorders where antidepressants are being used) as well as increasing incidences of depression worldwide and increased disease awareness/recognition of the disease.	Data reflecting this phenomenon should be included/taken into account.	The increasing use of antidepressants could certainly be related to several factors other than depression. It is not within the scope of this document to perform a detailed analysis of this phenomenon. The statement has been removed from the revised document as it is currently irrelevant to the specific research questions addressed by the HTA.
	Chapter 1, introduction	In Chapter 1 it is stated that most patients receive their medication from general practitioners and in the summary it says that “in clinical practice mild depression is more commonly encountered”	It is recommended to consider that more severe forms of MDD are mostly treated by specialists and general practitioners might see patients after symptoms have decreased for maintenance treatment.	We reported on prescription practices as reported in the literature. Whether patients are treated by general practitioners or mental health specialists depends on multiple factors including and not limited to, as you said, the severity of the patient’s condition as well as specific health system and clinician related factors. However, it is beyond the scope of this document to assume or address the referral mechanisms or clinical practices related to MDD.

	Chapter 1, i. antidepressants vs. placebo	Highly selected populations are indeed limiting generalizability of findings but in the sense of underestimating the beneficial effects of antidepressants (see recent publication Maslej MM et al. JAMA Psychiatry 2020).	It seems that personalization of MDD treatment can maximize treatment response and therefore mixing up different types of depressed patients might smooth out the real efficacy of antidepressants. It is recommended to take into account individual responses to different types of antidepressants and correspondingly depression subtypes.	The idea of personalized treatment is very interesting. However, in this project we will not be able to investigate the effects of personalized medicine. Nevertheless, we will try to identify factors influencing efficacy and safety as far as the data allows. This will allow us to perform stratified subgroup analyses according to these specific factors.
	Chapter 1, ii. antidepressants vs. psychotherapy	Why does the scope not mention the controversy about the efficacy of psychotherapy that is also discussed in literature (less effective than assumed)?	It is suggested that the scope should include the discussion about effectiveness of psychotherapy, for example (Cuijpers et al., Epidemiol Psychiatr Sci. 2019, 28:21–30).	We revised the document and included more details.
	Chapter 1, ii. antidepressants vs. psychotherapy	There is a difference in what type of depression the patient has and the beneficial effect of either pharmacotherapy or psychotherapy on that specific depression. For instance, patients with chronic depression without childhood trauma respond better to antidepressants and patients with chronic depression with childhood trauma respond better to psychotherapy (Nemeroff et al Proc Natl Acad Sci U S A 2003;100:14293-6).	Such data about differential effects of either treatment should be included in the scope.	It is true that the effect of antidepressants differs across different types and underlying etiologies of depression. For that reason, we are including studies with only major depressive disorder and excluding those with persistent depressive disorder (i.e. chronic and treatment resistant depression).
	Chapter 1, iii long term effects	Data against the long term use of antidepressants is presented.	The choice of at least 12 weeks studies is contradictory in the PICO paragraph.	The focus of the HTA will be to examine the effects of antidepressants extending beyond the acute phase of treatment. As such, we will include studies that have a follow-up duration more than 12 weeks.

	Chapter 1, iii long term effects	Chapter iii “long term effects” suggests that long term treatment with antidepressants might have negative effects.	It is recommended to discuss the mentioned data in more detail as do almost all guidelines, national and international ones alike, e.g. German S3 Guidelines recommend long term maintenance treatment.	We are aware that almost all national and international clinical guidelines recommend long-term maintenance treatment. However, the underlying evidence is either not very clear or there is no consistency between the clinical guidelines due to the lack of strong evidence. As such, an examination of the effects (whether beneficial or harmful) of antidepressants in the continuation and maintenance phases of depression management as proposed in our document is warranted.
	Chapter 1, iii long term effects, paragraph “ harms of treatment”	Chapter iii “harms of treatment” suggests that there is “a need for a benefit/harm assessment to justify the net benefit of the use of antidepressants”.	The benefit/harm assessment for all approved medicinal products have already been done by local and international agencies like Swissmedic. Marketing authorizations for approved medicinal products are subject to renewals where a new benefit/harm assessment is done by Swissmedic. Renewals used to be done every 5 years and are now done at least once in the lifecycle. In addition to that substance, specific safety data must be submitted regularly to Swissmedic reflecting national and international substance specific safety data (PSUR-PBRER).	We agree that individual antidepressants undergo a benefit-risk assessment by Swissmedic and it is not the purpose of the HTA to interfere with this regulatory process. However, most risk-benefit assessments are qualitative assessments. They may calculate some effects in terms of the number needed to treat (NNT) for the benefit outcomes and the number needed to harm (NNH) for the harm outcomes. However, with such approaches it would not be feasible to assess if a group of patients gets a net benefit from the treatment. In this HTA, we will perform a benefit-harm analysis that considers all positive and negative outcomes on the same scale and assess whether the benefit outweighs the harm or vice versa.
	Chapter 1, iii long term effects, paragraph “ harms of treatment”	There is convincing evidence that antidepressants decrease suicidality in older patients (>24 years) and do not increase it in younger patients (18-24) (Näslund et al. Br J Psychiatry 2018).	Decrease in risk of suicidality shown with antidepressants should be included in the discussion about benefit/harm assessment.	Thank you for your suggestion. We will consider risk of suicidality as a potential outcome in our analysis..

	Chapter 1, iii long term effects, paragraph “patient preferences”	It is stated “…people generally preferred psychotherapy over antidepressants”. Literature shows that indeed the preferred treatment from the patients perspective leads to a better effect. This preferred treatment might be either pharmacotherapy or psychotherapy and if a patient who prefers pharmacotherapy receives psychotherapy he/she will improve significantly less well than when treated with pharmacotherapy or vice versa (Mergl et al, Psychother Psychosom 2011;80:39-47).	This concept as well as the fact that Swiss guidelines already include the idea of taking into account the patient preferences when choosing a treatment, should also be included in the scope.	As you mention, patient preferences are extremely pertinent in choosing treatment and have been highlighted in Swiss and other international guidelines. Within the context of an HTA, we have proposed that this could be possibly explored in a preference eliciting study as part of a quantitative benefit harm assessment.
	Chapter 3, i. Population	It is unclear if the chosen population does reflect the majority of patients using antidepressants in Switzerland. MDD is an episodic disease and patients suffering from recurrent MDD are excluded.	A detailed rationale for the choice of population should be added.	We agree that a significant proportion of the population with major depression experience recurrent episodes. We have amended the population of interest to reflect that. On the other hand, patients with chronic and treatment resistant depression (definitions included within the revised document) will be excluded as they represent a category of depressions separate from major depressive disorder.
	Chapter 3, ii. Intervention	“Only at least 12 weeks studies should be considered”	Study duration with 6-12 weeks should be included in this HTA. This time range correspond to several therapy guidelines for acute treatment in MDD and is used in international reviews (for example: Cochrane reviews). There is no reason to exclude treatment of acute MDD. On the contrary, treating acute	As previously mentioned and as you also state below, extensive literature reviews and meta-analyses have already been performed to assess the effectiveness of antidepressants in the acute phase (<8-12 weeks). As such, we tried to avoid the duplication of pre-existing work. The main

			MDD is obviously highly relevant from a clinical point of view. Treatment of acute MDD is mostly studied in 8 weeks trials as this is an EMA standard for approval of antidepressants.	aim of this HTA is to expand the evidence of the effectiveness of antidepressants beyond the acute phase only. We are not planning on excluding studies with acute treatment; however, as we are interested in the mid-long term perspective of these therapies, we will only include studies with a longer follow up duration. The effect of treatment duration on outcomes will be explored through subgroup analyses.
		Access to non-pharmacologic therapies is of course beneficial and highly relevant. It should be considered that severely ill patients often cannot benefit from psychotherapy due to their severe stage of MDD, though. In these cases, first antidepressants are used to further enable patients to benefit from psychotherapy as well.	The quick onset of symptomatic recovery is thus relevant for further treatment which is why it is recommended to include all RCTs, also those in acute MDD.	
	Chapter 4, evidence synthesis	Is another systematic review based on the same existing literature that has been analysed over and over going to contribute to a clearer picture on the matter?		We agree that the effectiveness of antidepressants in the acute phase has been comprehensively examined. However, the possible proof or lack of effectiveness of antidepressants during the initial phase of treatment is not a reason to not address other aspects and domains. This includes their long-term use while taking into consideration both benefits and harms. As antidepressants are often taken for a long period of time that extends beyond the acute phase, an extensive analysis of the available evidence from a long-term perspective is needed.