Cochrane Common Mental Disorders Group | Protocol feedback summary

Title of protocol: U04 Withdrawal of antidepressants (Now changed to "interventions to help patients withdraw from antidepressants")

	Peer Review Comments	Authors' Intermediary Response	Authors' Response
#	**1. General Comments**		
1.	**Editorial base - Lindsay Robertson (comment on v1):** The protocol does not have the level of detail required to meet the MECIR standards. I would suggest authors read the standards and re-write their protocol so that they meet the necessary requirements.	Done. **Ed Base check – Jess Hendon (comment on v2 & v3): Still concerns that protocol does not meet MECIR standards.**	The MECIR manual takes up 61 pages. As we cannot know what precisely you have in mind, we have addressed each of your specific comments below.
2.	**Editorial base - Lindsay Robertson (comment on v1):** The title is too vague and should be more specific.	Title changed from "withdrawal of antidepressants" to "interventions to help patients withdraw from antidepressants"	
3.	**Steph Sampson, Research Fellow, University of York (SS) (comment on v2):** This is really important proposal, and it has the potential to be a very informative and influential review. However, there are substantial changes needed in order to achieve a coherent and strategic protocol for a systematic review. The authors raise some interesting points and arguments worthy of further exploration in their background, however some of these arguments are misplaced in the context of this review, i.e. helping people withdraw from antidepressants and the interventions that can help them and their clinicians do it in a safe way, whilst recognising both the risks and benefits.	Our comment: Please explain how it can be misplaced to talk about helping people who want to withdraw from drugs to withdraw? We do not understand the comment. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Suggest the authors simply clarify that the intervention is offered where either the clinician or patient are wishing to safely and comfortably withdraw from antidepressants?	We have added, to "Description of the intervention": It can also be the clinician who takes the initiative to safely and comfortably withdraw the medication.
4.	**Steph Sampson (comment on v2):** The main problem is the confused scope. The authors are seemingly proposing a review that will examine the effects of interventions intended to help people (undefined populations) withdraw/ taper-off/ reduce doses of antidepressant medications (undefined). This would be great; however, the authors should define the populations of interest for the review for transparency sake and for replicability.	Not "seemingly". We are proposing a review that will examine the effects of different ways/interventions to help patients come off antidepressant drugs. Interventions to help patients reduce/lower doses fall outside the scope of this review. We don't plan to define/divide the population of interest in such ways, as the population has already been clearly defined: People on antidepressant drugs who, for whatever reason, wants to come off. The patients' reasons for wanting to come off is irrelevant and therefore not a defining feature in our protocol or in the literature search, as the current one is capable of finding RTCs with all types of patients.	See just above. We now write that both the patient and the clinician can wish to withdraw the drug. We write in our review: Types of participants People taking antidepressant drugs who wish to come off them. We are interested in withdrawal irrespective of age, sex, setting, diagnosis of depression, types of

		Co-ordinating Editor Rachel Churchill (follow-up comment on v3): As above, the authors simply needed to clarify that these interventions are appropriate where a decision has been taken that this is right for the patient (which we assume to be the case although this is not explicitly stated). It is however also necessary to clarify which users of antidepressants this review is going to be relevant to (even if it includes all of them). For example, we would want to be clear whether the population of interest includes long-term users of antidepressants, is in receipt of high and/or low doses, etc. We would also not expect to see the effects of these interventions evaluated in one analysis for all patient groups, age groups, and so on, so the handling of these needs to be clearly stipulated. This could be a very heterogeneous group of patients withdrawing from antidepressants for a variety of different reasons (including long-term users, people experiencing unacceptable side-effects, treatment non-responders, treatment responders, people with specific health/life transition reasons - such as poly-pharmacy and drug interaction issues, physical health conditions, pregnancy – and so on). These factors could impact on the effectiveness of the interventions under review, which is why it is important that these issues are considered. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree that this level of clarity is required; would also add that they will have been on antidepressants for various indications, and as stated it is ok to include all but in terms of defining how the analysis will be done, this would be a further consideration.	antidepressants, or the reason for wanting to come off. We believe there is no need to go into the level of detail suggested by Churchill. As there are very few studies, it is most helpful for the users of our review that we are as broad as possible in our inclusion criteria. If the data allows this, we may then in the review address some of the comments Churchill suggests. As the withdrawal symptoms can occur for any type of patient, drug or dose, this also suggests a broad, and not a narrow approach.
5.	**Steph Sampson (comment on v2):** However, while reading the background section it becomes clear that the authors are leaning more towards a stance that assumes all patients (regardless of diagnosis) are dependent on ADs, which introduces an argument framing patients as 'addicts', an argument that is not fully explored nor justified sufficiently with relevant references from the literature in addiction/ dependency.	Our comment: We do not say that all patients have become dependent. We only speak about patients wanting to come off their drug. That antidepressant drugs can cause withdrawal symptoms when reduced in dosage is not something to "lean towards", but a well-established scientific fact. We do not use the word "addict" in our protocol, as patients generally do not consider themselves as such. However, patients experiencing no effect who wish to come off, but can't do so because of withdrawal symptoms can rightfully be categorized as being	We have carefully gone through the Background section once again and have made changes as suggested. We have inserted subheadings in Background as suggested. We have changed ""Withdrawing from psychiatric drugs can be very beneficial" into:

		dependent on continuous drug-intake, as this keeps the withdrawal symptoms (which can be very unpleasant) at bay. That is, the absence of withdrawal symptoms becomes literally dependent on continuous intake of the drugs – with no connotations of being addicts in the traditional sense. As you can read in Kessing 2005 (which is in our review), the patients generally agree on this. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** The authors may have misunderstood the underlying issue in relating to this feedback which simply relates to the tone of the writing. It has not been suggested that symptoms associated with AD withdrawal are not well-established. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** We agree that symptoms associated with AD withdrawal are well-established. It would be useful for authors to ensure they present the evidence in a succinct and clear way to avoid any possibility that readers of the review might assume the review authors are taking a stance in one particular direction. I would suggest that the background could be shortened, with careful attention to ensure a balanced representation of the evidence, and the context in which AD medications are being withdrawn from i.e. When ADs are used, the types of ADs used, the (relative) evidence about effectiveness of ADs, side effects, evidence about effects of long term use. A concrete example: presumably there might be a group for whom coming of their medication is not beneficial (as opposed to the statement "Withdrawing from psychiatric drugs can be very beneficial", so in this case it might be stating it as "Withdrawing from psychiatric drugs can have beneficial effects for some patients".	"Withdrawing from psychiatric drugs can have beneficial effects for some patients." We have deleted: ", which is a clear sign of beneficial effects of becoming drug-free." We have changed "abstinence depressions" to "withdrawal depressions." We have changed "Some patients refer to the myth about a chemical imbalance in their brain being the cause of their disorder" to "Some patients refer to the discredited hypothesis…" We have deleted the bit in green in this sentence: "Since millions of patients can be expected to have become dependent on antidepressant drugs worldwide (Davies 2018) (because the withdrawal symptoms keep them on the drugs even if there is no effect and many harms)" We think the background is very useful for patients and clinicians, as few people are aware of the issues we describe. Hetrick suggests we write about when the drugs are used, which drugs, their effectiveness, etc, but this is not relevant for a review of withdrawal, see our previous comment under point 7 below, middle column.
6.	**Steph Sampson (comment on v2):** How do the authors plan to define patients who are explicitly dependant/ addicted to ADs versus those who take ADs as part of their prescribed medication and would not consider themselves to be dependant but may want	We have no such plans. We disagree that our category "antidepressant medications" is undefined, as the drugs of interest simply are all antidepressant drugs. Our goal is to provide help for patients undergoing psychiatric drug withdrawal –	See above, point 4, right and middle columns.

	to take lower doses/ feel as though it's the right time to come off the drugs. There is a difference in these populations, and the authors may find it difficult to find RCTs including the latter. The authors need to be careful in defining their population and with the language used, which can come across as generalising and reductive.	whatever the barriers and difficulties may be – irrespective of type of antidepressant drug. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Not sure I understand the authors' response here. It doesn't seem to relate to the feedback item which again refers to issues about the clarity of the population of relevance. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree; it is important, as above to ensure that the population(s) are well defined.	
7.	**Steph Sampson (comment on v2):** If the authors are going to introduce 'withdrawal effects' of ADs, it would help the reader if the current evidence for the effects of ADs were addressed – for example, see Cipriani 2018, who offers the most recent network meta-analysis of 21 antidepressants. Addressing the evidence and the ADs of interest will help clarify the scope of the review for the readers and the ultimate consumers of the review as well as the drugs they are considering whether or not to prescribe as a clinician / take as a patient.	Our comment: The scope and aim of this review has been clearly defined: How to help patients withdraw from antidepressant drugs in the best and safest way. This is not a discussion of the efficacy of antidepressant drugs. The drug-placebo difference has repeatedly been found to be clinically insignificant, latest by Cipriani 2018 who found an SMD of .30, which is way below both the evidence-based cutoff for clinical significance of .875 (Leucht 2013; Moncrieff & Kirsch 2015, corresponding to "minimally improved", which actually isn't even clinically significant). A list of SMDs in several meta-analyses of the drug-placebo difference is presented below. See also Jakobsen 2017, Kirsch & Sapirstein 1998, Khin 2011, and Gibbons 2012. Kirsch 2002, 2008: 0.32 Nice 2004: 0.34 Turner 2008: 0.31 Fountaloukalis 2010: 0.32 Fournier 2010: 0.30 Cipriani 2018: 0.30 Could the editors please present their reasoning behind connecting the issues of withdrawal symptoms of ADs with the efficacy of ADs? These are two completely different topics and we have no interest in further scientific exploration of the latter in our review. There are several Cochrane reviews that deal with the clinical effect.	See middle column, our previous reply. Churchill suggests we should write about the context in which antidepressants are prescribed, that "antidepressants do have a place in the treatment of depression (some people find them of value)," that "some antidepressants may be more effective than others." We do not agree that a review about withdrawal is the right place to take up all this. It would be a long discussion because it is controversial whether these drugs have a relevant effect in depression, which we carefully explained in the middle column. Our review should not be a kind of "advertisement" for these drugs but should be strictly factual. Cipriani's review that claimed that some SSRIs are better than others is not reliable, which we and others (there are also papers in press) have explained.

		Helping patients and clinicians in considering whether or not to prescribe antidepressant drugs, or which drugs to prescribe (as the editors suggest here), is absolutely outside the scope of our review. The Cochrane Collaboration is about helping patients, and we are trying to help the many patients who want to come off psychiatric drugs but experience difficulties and barriers in doing so. The very fact that this population of patients are organizing themselves in survivor groups and various withdrawal-related initiatives/projects around the world is a clear sign that such help is needed. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** The feedback was not intending to suggest that the authors should support decision-making about choice of antidepressants in terms of efficacy; merely that they should acknowledge the context in which antidepressants are prescribed, that antidepressants do have a place in the treatment of depression (some people find them of value), a range of drugs with antidepressants properties are available (which could guide their inclusion criteria decisions), that some antidepressants may be more effective than others (which is important in terms of treatment decisions – including whether or not to consider withdrawing), that this could impact on their acceptability to patients (in terms of potential side-effects), as well as potentially impacting on the potential withdrawal effects (which is what these interventions are trying to mitigate). This is important contextual information for readers and we think it should be included. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed.	
8.	**Steph Sampson (comment on v2):** References on rates of dependency for ADs in general, as well as by drug would strengthen this protocol.	Our comment: We do not find this relevant considering the focus for our review. Paragraph slightly changed, and references added (Ostrow 2017 and Davies 2018), see protocol. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):**	We already did give rates of dependency in Background (about 50%). It is therefore not correct that such figures do not exist. They do, and they have been published.

		As above. Context needs expanding as it's important information for readers. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree: I noticed no prevalence was given – would be good to state this or that such figures do not exist and then provide evidence that this issue exists via means authors have currently stated.	
9.	**Question asked of consumer peer reviewer:** ***Can you understand the title? If not, can you identify which words or phrases are difficult to understand, or could you suggest any improvements to the wording? Does the title reflect what the Cochrane Protocol is about (you will need to read further before you can answer this)? If not, please explain.*** **Karen Morley, consumer peer review (comment on v3):** In the light of some comments in the Background section (see below) I find it ambiguous. Does it mean interventions to support patients who are withdrawing from antidepressants, or does it include an implication that all patients who are taking antidepressants and wish to come off should be helped to withdraw from them? As a consumer I would welcome interventions that can make withdrawal as a result of fully informed, evidence based, shared decision making, tolerable and safe in the short and long term		The editors have changed the title, so it has already been changed: "Interventions to help patients withdraw from antidepressants." We believe this covers very well what our review is about.
	2. Terminology		
	Is the terminology acceptable?		
10.	**Editorial base – Lindsay Robertson (comment on v1):** What are SSRIs? When using abbreviated terms, the full name should be stated in the first instance.	Abbreviations explained. **Ed Base check – Jess Hendon (comment on v2): Actioned**	No response requested
11.	**Steph Sampson (comment on v2):** Could the authors avoid use of terms like 'neuroleptics' which is more out-dated terminology and use 'antipsychotics'.	The prefix "anti" suggests curative properties, like antibiotics for bacterial infections. This is not the case with any of today's psychiatric drugs. The effect of neuroleptics is highly unspecific; it is the same in healthy people and animals as in psychotic patients; and im seriously biased trials it is not even large enough to be of clinical relevance (Leucht 2005). **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** We do not think it would be helpful to enter into epistemological debate, but simply to set the protocol in language that is current and familiar to patients and clinicians. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree.	We have changed neuroleptics into antipsychotics as requested, although these drugs do not have specific antipsychotic properties but are major tranquillisers, which they were first called.

12.	**Steph Sampson (comment on v2):** Language can be accusatory and overly declarative. For example, fourth paragraph of the background, 'It often confuses clinicians that withdrawal symptoms and disease symptoms can be the same, and they often resume the full dose of the drug when patients experience too unpleasant withdrawal symptoms.' Can the authors please reframe language and provide references for statement of fact?	Paragraph reframed, see protocol. See Rosenbaum 1998 for evidence of abstinence depressions: 36 % of patients on paroxetine, 30 % on sertraline and only 6 % on fluoxetine (which has a much longer half-life and therefore fewer withdrawal/abstinence symptoms) experienced a Hamilton increase of >8 when abruptly switched to placebo for 5-8 days under double-blind conditions. See also Nielsen 2011 and Fava 2015 for two comprehensive systematic reviews and lists of the most commonly identified withdrawal symptoms of SSRIs. Comparing these with the diagnostic criteria of depression reveals a clear overlap. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** The authors are very aware that convincing the editorial team of the importance of this topic is not necessary. Details justifying the approach to be taken in the protocol are not provided for our benefit, but for the benefit of readers and decision-makers. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree; it is good to see references added, although those cited here are not relevant to the point being made about clinicians being confused and resuming the full dose. It is important that language is addressed more comprehensively and this is from the point of view of ensuring the reader understands the issue (how important this review is more patients) and isn't distracted from this by taking the view that the review authors are taking a stance in one particular direction.	See above. We have changed the Background so that it is clear that we do not take any "positions" but merely want to help patients and clinicians with drug withdrawal when that is desired. The facts we convey under Background are helpful for understanding the issues.
13.	**Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** The only other comment I have is about the use of the word "patient", which I know is commonly used in our reviews, although it is less common in reviews of younger people because of consumers who have rightly stated that they don't want to be positioned in this way (within the medical model as a passive recipient; deficit model).		Empirical studies have shown that patients prefer to be called patients. They don't like being called consumers, clients, etc. See, for example: Deber RB, Kraetschmer N, Urowitz S, et al. Patient, consumer, client, or customer: what do people want to be called? Health Expectations 2005;8:345-51.
14.	**Question asked of consumer peer reviewer:** ***a) Is the Cochrane Protocol reasonably easy to understand? Is the technical language used appropriately, and where possible, explained? If not, which sections need to be clearer and can you suggest any improvements? Is any language insensitive to consumers? Please suggest alternative phrases if possible.***		We have changed the wording, as also suggested by the editors, see above. We

	Karen Morley (comment on v3): As I have noted above, I find the expression is often imprecise, sometimes ambiguous and sometimes insensitive to the anxieties of patients. Emotive language is included. Consequently the style seems colloquial rather than dispassionate and scientific.		have carefully documented the facts we present.
	3. Background		
	Does the Background include the biological and health care rationale for the intervention under study?		
15.	**Editorial base – Lindsay Robertson (comment on v1):** The background needs work as it doesn't set the scene as well as it could. How many people are on antidepressants? How do they work? What are the different types (e.g SSRIs, SNRIs, TCAs, MAOIs)? Why is withdrawal so hard? What are the side effects? A more structured background would provide a better description of the condition and intervention, and highlight the need for this review.	We have revised the background. We disagree that going into detail about how the different types of antidepressants work (which, in addition, is controversial) has any relevance for our review. We have described the most common withdrawal symptoms. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** I believe that the subsections sections provided within RevMan are helpful for addressing the point being made here (below); the text provided before the first subheading could be moved to sit in relevant subsections.	See above.
16.	**Steph Sampson (comment on v2):** The first sentence is very broad and uses language that does not reflect the content of the results from the references cited. E.g. the Kessing 2005 study presents results from a sample of N=1005 from Denmark, with 56.7% agreeing that it is difficult to stop taking ADs when you have been using them for a long time. This isn't representative. Suggest the authors include more relevant/ up to date references here, and qualify statements with more suitable language, for example 'For people who have been taking antidepressants for a long time, stopping these drugs and ultimate withdrawal can be a difficult process, and previous research has shown….etc.'.	Our comment: A substantial number of patients say that it is difficult to stop taking the drugs, which leads to unsuccessful attempts at coming off as shown in, for example, Breggin 2012, Breggin & Cohen 1999, Lehmann 1998, Gøtzsche 2015, Whitaker 2010, Glenmullen 2005 and Glenmullen 2000. See also just above. Language revised, see protocol. **Ed Base check - Lindsay Robertson (comment on v3): The first sentence has been removed as recommended but now there is no description of what previous research has shown.** **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** As above. This information is important for readers. The authors need to expand the description presented in their protocol to include this literature as appropriate. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree.	We detail under Background what previous research has shown, in fact so much that Hetrick suggested we shortened the Background (see above), and we still quote Glenmullen, etc.

17.	**Steph Sampson (comment on v2):** Could the authors clarify that withdrawing from ADs can have 'beneficial effects', as opposed to simply being 'beneficial'? As there is evidence to say that receiving ADs can have beneficial effects too.	The main beneficial effect of becoming drug-free is the absence harms. It is a well-established scientific fact that all psychiatric drugs can cause harm. Furthermore, long-term studies of psychiatric drugs consistently show better recovery rates in the non-medicated group or the group that managed to come off. Recovery is indeed a beneficial effect. Our review is not about beneficial effects of antidepressants; many Cochrane reviews deal with this. **Ed Base check - Lindsay Robertson (comment on v3):** I agree with the reviewers comments: There are beneficial EFFECTS of both being on and off ADs. Saying that "withdrawing from ADs would be beneficial" suggests that ADs only cause harm and ignores the benefits it has on one's depression. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** This needs to be addressed in the protocol – the tone of the language needs to demonstrate equipoise; it would be unfortunate if the conclusions from a review of this importance were to be undermined because the language used suggests a starting position on the value of antidepressants. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree (as per comments above).	We have changed this, which was also suggested by Hetrick (see above). Our review is not the right place for a discussion of what the benefits of antidepressants are and whether they are relevant for patients (see above). We do not write anywhere what the magnitude of the effect is because this is not relevant for a review about withdrawal. We therefore do not take any position on this in our review. In contrast, it seems to us that the Cochrane editors have taken a position on this.
18.	**Steph Sampson (comment on v2):** Can the authors provide more detail on the Wunderink 2013 study: i.e. that there was indeed twice the recovery rate in people receiving a dose reduction intervention compared with people on maintenance therapy at seven year follow up. However in this study participants were specifically in the early stages of remitted first episode psychosis. The authors have further omitted any reference to the original results of this trial (Wunderink 2007) which found that, in the short term, the discontinuation group led to significantly more relapses, with only 20% of participants successfully discontinued. The 7-year follow-up presents really interesting findings, but needs to be put in context by the authors in order to present a balanced	Paragraph revised, see protocol. Wunderink 2013 is a more recent follow-up than Wunderink 2007, which is why we primarily refer to that. It is a valid point to emphasize that the withdrawal group deteriorated for a while before getting better, but this only demonstrates that it can take a very long time before the drug-induced brain changes normalise. The end result is much more important: Better recovery rates for patients not on drugs compared with so-called "maintenance therapy" shows that the drugs maintain the disorder, rather than cure it. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Again, I think the authors need to be careful to demonstrate objectivity in their presentation of the evidence and that any assertions are properly substantiated. More importantly, for	Based on previous comments from the editors, we also quoted Wunderinck 2007 and tried to explain why the patients initially got worse during withdrawal. We believe our suggestion of why this was the case is very relevant for our review but will delete the bit in green if the editors prefer this: "Another trial, of patients with schizophrenia treated with antipsychotics and currently in the early stages of remitted first episode psychosis, showed that more patients (twice as many) had recovered in the dose

	view of the risks as well as the benefits of withdrawal over the stated time period.	patients, the process and experience of withdrawal in both the short and long term is highly relevant and should not be ignored. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree: I think the point is that all of this information needs to be presented (and authors have now included information on the 2007 study) so that people are aware of what the course might be (potential for harm as well as benefit) both in the short term and the long term. This particular paragraph ends with statements that are not referenced and appear to be opinion only; the presentation of the evidence might be sufficient without trying to suppose why there was an initial deterioration. The last statement belongs in the section about 'why it is important to do this review'. Of note, the patients in this study did not receive any psychological therapy or other help during the withdrawal process and the habituation to the drug-free state. How to help patients so that they do not deteriorate (which primarily is a question of reducing or even eliminating withdrawal symptoms) is the focus of our review. **Ed Base check - Lindsay Robertson (comment on v3):** Authors have revised this paragraph as suggested.	reduction/withdrawal group than in the maintenance group at seven years of follow-up (Wunderink 2013). In an earlier follow-up of the same study (Wunderink 2007), the dose reduction/withdrawal group deteriorated initially before improving, suggesting the transition from medicated to drug-free is a difficult process for patients to go through. The patients in this study did not receive much psychological support or other help during withdrawal, which might be the reason for the temporary deterioration. How to help patients so they do not deteriorate but go straight to improving is the aim of our review.
19.	**Steph Sampson (comment on v2):** Fifth and sixth paragraphs – Not sure what this section is trying to say and why it's relevant here, and the references cited (Gibbons 2012) doesn't seem to justify what's being said. Are the authors arguing that withdrawal techniques are less likely to be successful due to misunderstanding/ misdiagnosis of clinicians who confuse withdrawal symptoms with re-emergence of depression? If so, can the authors be more structured their arguments, for example by introducing a relevant section that examines the various reasons that discontinuation/ withdrawal can be difficult, for both clinicians and patients?	Gibbons 2012 was indeed misplaced. Paragraph revised, see protocol. What we are arguing here is the same as in the second paragraph under "2. Terminology" above. For a list of withdrawal symptoms making discontinuation/withdrawal difficult, see Nielsen 2011 and Fava 2015. Note also the huge overlap between withdrawal symptoms of SSRIs and benzodiazepines in Nielsen 2011, which is relevant considering that benzodiazepines are officially recognized as addictive and very difficult to come off and not recommended for long-term use, which isn't the case with SSRIs.	See above. We have revised the Background several times and believe it is very good. If Hetrick wants further changes, we will need to know exactly which ones.

		In addition, we introduce the idea that coming off psychiatric drugs can be difficult for various psychological and emotional reasons, for example anxiety, uncertainty, worry of relapse, poor emotion regulation skills and need of social support, as is evident from qualitative interview studies such as Lucassen 2014, Bosman 2016, Leydon 2007 and Verbeek-Heide & Mathot 2006. Furthermore, valuable information on the experienced difficulties and barriers of psychiatric drug withdrawal can be found in various patient reports of the process. These reports appear especially in books on the subject, as for example Breggin 2012, Breggin & Cohen 1999, Lehmann 1998, Gøtzsche 2015, Whitaker 2010, Glenmullen 2005 and Glenmullen 2000. In addition to the medical aspects (i.e. withdrawal symptoms), many of these stories point to psychological, emotional and existential aspects of the transition from a medicated to a medicine-free state. These have not much to do with dose reductions and tapering schemes per se but are just as relevant for our review. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** All of this additional information has been added; I believe it needs further synthesis and could be more succinctly written. It also all belongs within the relevant subsections of the background (which I helpful in terms of structuring the background and ensuring all the information that provides relevant context and leads the reader to understand why this review is necessary is presented).	
20.	**Steph Sampson (comment on v2):** Seventh paragraph: can the authors provide a more detailed background of possible withdrawal symptoms? 'Psychological dependency can also be important, and some patients refer to the myth about a chemical imbalance in their brain being the cause of their disorder and therefore also the reason for not daring to stop (Lucassen 2014).' – Can the authors be more balanced in their argument here?	Our comment: We do not understand the comment. Presenting facts about psychological barriers have nothing to do with being balanced/unbalanced. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** The point the referee is making here is that there may be justification for these concerns. The authors' argument would be more powerful if presented more objectively. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):**	See above, we have followed the editor's advice about this and no longer use the word "myth" about the chemical imbalance.

		Authors need to not assume that the reader doesn't also believe this myth but rather present the argument: "people on antidepressants may believe that this is necessary because they have a belief that the difficulties they are experiencing are due to a chemical imbalance in the brain." It probably isn't relevant to the purposes of the review to present the argument about the cause or not / mechanisms of action of antidepressants with regard to the cause of disorders. I note the use of the word 'disorder' in terms of how that positions this piece of work. For elaboration of what we here call "psychological dependency", see above. For a list of withdrawal symptoms, see Nielsen 2011 and Fava 2015.	
21.	**Steph Sampson (comment on v2):** Can we have more detail on the types of antidepressants this review is looking for? This is important not only for the reader, but also for the authors when it comes to devising search terms for the review.	See above. We looked at all antidepressants. Type of antidepressants is not important when devising search terms, as the MeSH term function allows us to search the database for all types of antidepressant drugs in the same search, which is exactly what this review is about: Patients on antidepressant drugs – all types of antidepressants. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** From an IS perspective, the types of drugs with antidepressant properties will need to be clarified. Readers will also benefit from having this information (from their response, it sounds as though the authors have already completely the work).	See above where this comment was also raised.
22.	**Steph Sampson (comment on v2):** A more balanced assessment and appreciation of the various reasons a person may want to discontinue/ withdraw from antidepressants is needed, as the Background currently reads as patients being dependant. How about economic reasons/ cost for individuals? Stigma?	See above. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** It would be good to see, what is contextual information, about why people might want to discontinue/withdrawal, from their perspective, and clinically.	See above where this comment was also raised.

23.	**Steph Sampson (comment on v2):** It would be helpful if the authors planned a more organised structure to the background section in order to create a strong, coherent argument. For example, starting with the problem, which the authors argue is an over-reliance on these drugs (how many people are on ADs/ what types of ADs are there/ what is the evidence for their efficacy/ what are the different SE profiles/ what are the different withdrawal symptoms), reasons for wanting to withdraw or discontinue them (SEs/ economic or cost-related reasons/ stigma-related, etc), and broadly the population that is the focus of this review (depression/ anxiety/ SMI, etc). It is important that this is delineated, particularly because under 'Description of the condition' the authors state that 'The patients' condition is best described as drug dependence'. This has implications for any search terms the authors devise – at a guess it will be difficult to find RCTs on tapering/ withdrawal techniques for participants who are classed as 'drug dependent', and they would more likely be people with 'depression/ anxiety/ schizophrenia', etc.	See above. We have discussed all these points throughout this document. It is not relevant to state how many patients take these drugs. Whether it is 300 million or 500 million world-wide doesn't matter **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** We have asked for a more structured and coherent presentation of these components. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree; note my comments on using the subheadings (rather than a large block of text prior to the subheadings).	We have inserted subheadings in Background as suggested.
24.	**Steph Sampson (comment on v2):** Description of the condition Can the authors provide references for drug dependency on ADs, as well as for the proposed benefit of psychotherapy for this population? More detail needed here, particularly if the authors are adopting an addiction/ dependence model in patients receiving ADs.	See above. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree that this needs to be clarified in the text, with much more structured and synthesised descriptions provided as per suggestions from editorial team)	See above. The benefit of psychotherapy in depression is outside the scope of our review.
25.	**Steph Sampson (comment on v2):** Description of the intervention Systematic review evidence has been omitted that could be relevant in framing this part of the background: please see Sampson S, Mansour M, Maayan N, Soares-Weiser K, Adams CE. Intermittent drug techniques for schizophrenia. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD006196. DOI:	Intermittent drug techniques for neuroleptics are outside the scope of our review, which focusses on how to help patients come off antidepressant drugs. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** I note that the authors have included evidence from trials of neuroleptics in people with first episode psychosis and while these are outside of the scope of this review, as per the way authors	We comment on Wunderink's trial of withdrawal of antipsychotics because this knowledge is relevant also for withdrawal of antidepressants. We do not find it relevant to make the Background longer by commenting on intermittent drug usage in patients with schizophrenia.

	10.1002/14651858.CD006196.pub2. Even though this review looks at antipsychotic medication, there are various ways the authors approached discontinuation/ intermittent treatments that could be helpful.	have used the Wunderlink trial, citing such reviews as suggested again provides context for the reader and might be useful.	
26.	**Steph Sampson (comment on v2):** How the intervention might work More detail needed here. The authors need to specify how proposed interventions can work to benefit individuals, with more specific detail required. Again, for ease of understanding for the reader, and to help provide structure in search terms and identification of relevant studies. If interventions aren't fully pre-defined this can lead to a selection bias at the review stage.	The mechanisms of action of the different methods are irrelevant to know beforehand, as we have defined our interventions of interest based on their aim – to help patients come off antidepressant drugs. As we include everything, selection bias is not an issue. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** This is clearly a point of disagreement between us. This section needs further work. A diverse array of interventions is included. Readers need to understand why these might be helpful and what they might involve. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree.	See above.
27.	**Steph Sampson (comment on v2):** Why it is important do to this review What is the rate of prevalence and incidence of these adverse effects? And how long is 'long-term' for these AEs to become apparent? Again, much more detail is needed to present a balanced argument and investigate differences between patient populations and drugs. What are the most common, important reasons people want to come off ADs?	The Cochrane editors are making something, which is very simple, highly complicated. Our review has a very simple aim: to help patients come off drugs they want to come off. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** To be more specific, the aim is surely to evaluate the evidence for interventions to help guide decisions about helping patients who wish to withdraw from antidepressants. This isn't about making things complicated. This is about producing a robust, objective and informative evidence synthesis on an important topic to support decision-making. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree: establishing the importance of the problem, which is clearly defined and described (as well as the interventions for this, including how they might work) ensures that the review that is produced is robust.	This is about the section, Why it is important to do this review. We believe that what we wrote is accurate and helpful for the readers and do not understand what concerns the editors have, also because they are not specific about them. We write: "Why it is important to do this review About half of the hundreds of millions of people who take antidepressants have become dependent on them (Davies 2018; Gøtzsche 2015; Kessing 2005; Read 2014) in the sense that reducing the current dose will elicit withdrawal symptoms, which may lead to unsuccessfull attempts at coming off. It is evident that it would be beneficial for many patients' health to come off the drugs,

			particularly considering their long-term harms, which might involve irreversible brain damage (Breggin 2012; Gøtzsche 2015) including permanent sexual dysfunction (Healy 2018; Hogan 2014; Simonsen 2016)."
28.	**Nuala Livingstone - Associate Editor 'Mental Health and Neuroscience' Network, Review Production and Quality Unit, Editorial & Methods Department, Cochrane Central Executive (comment on v3):** The introduction to the Background section contains a large amount of information. However, much of it is beyond the scope of this protocol. The language used should also remain neutral and objective when summarising the background to the research question. The Background section should be concise but clearly defined description of the population and interventions of interest. (See MECIR Standard PR3). Specifically, the subheadings do not contain sufficient information regarding the different types of people in this population, the different types of interventions, and a more detailed explanation of how the different interventions may work.		See above, we have made changes to Background several times due to the advice from the editors.
29.	**Dr. Adam Todd - Reader in Pharmaceutical Public Health, School of Pharmacy, Newcastle University (comment on v3):** Thank you for the opportunity to review this interesting protocol regarding withdrawing antidepressants. I hope my comments are helpful to the authors. At present, I believe the background section is a little unfocused and could do with reviewing. The protocol is focused on antidepressants, but there is reference to other medications, such benzodiazepines, psychiatric drugs, and neuroleptics. Suggest that references to these medications are removed, as they have completely different indications, mechanism of action, and adverse event profile when compared to antidepressants. At present, I do not believe they add value to the protocol. I think the background section could also introduce the different types of antidepressants (SSRIs, TCAs, MAOIs, etc.). Given the different pharmacology of these drugs, it would be plausible that they have different adverse effects when reduced, discontinued. Also, it would be beneficial to introduce inappropriate versus appropriate use of antidepressants. The background appears to be a little one sided in that antidepressants are bad? For example, when are antidepressants indicated to treat depression, and for how long? What are the benefits of using antidepressants - and when should they be reviewed, reduced, stopped? This would add important context to the background, and give it more balance. Suggest that some of the terms used in the protocol are reviewed; for example, some people get terrible withdrawal symptoms could be replaced by some people get withdrawal symptoms that can negatively impact the quality of life of the patient. The paragraph listing all of the adverse effects is interesting, but it might be beneficial if the most common or those most clinically meaningful are outlined/discussed. The team might consider citing some deprescribing literature in the protocol, given the focus of the work is reducing or stopping antidepressant medication. See, for example, Scott et al., JAMA Intern Med. 2015;175(5):827-34		We disagree with this reviewer, see above where we have explained why. It is not relevant for a withdrawal review whether the drugs were used inappropriately. Background should not be a treatment guide for using antidepressants or a review of their benefits because whatever they are, some patients want to come off them and we wish to help these patients and their doctors. It is correct that some people get terrible withdrawal symptoms but we have now changed the word into severe. Please consider also the current debate in the UK about this where the Royal College of Psychiatrists were forced to change their position totally, after the College had previously trivialised these symptoms.

	Under the why it is important to do the review section, suggest adding in figures relating to antidepressant prescribing with more and more people prescribed these medications, it is clear that this work is important now, and will be even more important in the future.	Our list was not one of adverse effects of the drugs but one of withdrawal symptoms, which we believe is helpful. The paper in JAMA Intern Med is not a study and would not contribute meaningfully to our review. We do not think that numbers of prescriptions are relevant for a review of withdrawal. Whether there are few or many, some patients will wish to come off the drugs.
30.	**Question asked of consumer peer reviewer:** ***Does the background explain the topic clearly (i.e. are the healthcare need and intervention clear)? If not, which words or phrases are not clear, or how would you describe them? Does the background address the hopes and concerns of people considering the treatment? Is it clear "why it is important to do the review"?*** **Karen Morley (comment on v3):** I have concerns about some comments in this section. Here is a selection. The first sentence seems imprecise (and there is more imprecision elsewhere). For instance, how many is 'many patients'? What aspects of the withdrawal process are difficult? How long is 'a long time'? 'Stopping can be a difficult process due to withdrawal' is unclear and perhaps has a missing word. The sources used to support this statement are Kessing's paper about attitudes and beliefs of patients which refers only to hospital settings and a book by Peter Breggin who says in promoting it online, 'Nothing in the field of mental health will do more good and reduce more harm than encouraging withdrawal from psychiatric drugs.' This is a sweeping and fervid claim which, however sincerely held, disturbs me. It suggests a clear bias. A book of this apparent sort is far removed from a peer reviewed clinical study. Breggin is referred to throughout the protocol. I feel sources could be found that are more relevant and more impartial: I would have greater confidence in them. My understanding is that antidepressants and benzodiazepines have different mechanisms, but the Background yokes them together. In referring to patient helplines, it describes those who are prescribed them as a single population. A paper comparing side effects of these medications is referred to in paragraph 4. Benzodiazepines are highly addictive. Consumers might be misled by this comparison. Similarly, paragraph 2 refers to psychiatric drugs in general rather than antidepressants in particular. It also describes a study of patients with schizophrenia, withdrawing from neuroleptics, which I believe (although neuroleptics may be prescribed for	We wrote: "Many patients on antidepressant drugs have tried to come off them but have failed because the withdrawal process was too difficult for them to go through; especially for people who have been taking the drugs for a long time, stopping can be a difficult process due to withdrawal symptoms (Breggin 2012; Kessing 2005)." It is common to use such words without also giving a number. Considering the number of patients on the drugs, several hundred million, "many" must be millions. A "long time" just means the longer you have been on them, the more difficult it is to stop. We do not quote Breggin for what Morley says, and we give several references when we say how commonly patients experience withdrawal effects. We accurately quote one of our PhD students who found that withdrawal

	patients with major depression) are antipsychotics rather than antidepressants, so the successful withdrawal of these patients is unrelated to the protocol's population. I should prefer to read evidence about specific antidepressants and families of antidepressants. Another paragraph which concerns me is the one beginning, 'Some patients get terrible withdrawal symptoms when they try to stop…including some…which can frighten them.' 'Terrible' is an emotive word which might indeed frighten some consumers. I think language which might deter people from commencing medication or from attempting withdrawal would be best avoided. Perhaps 'severe' is an acceptable substitute. Also 'some patients' is imprecise, as is 'which can frighten them.' This is compounded by a paragraph-long list of identified withdrawal symptoms presented without information about their frequency, making them seem extremely alarming. I am unsure of the function of this list. I think the Background section should show more sensitivity to consumers who may well already be in a state of anxiety. In the sub-section 'Description of the intervention' the sentence, 'To our knowledge, there is no standard procedure…and not much science to guide us', possibly because of its expression, sounds like a guess. Is it possible to list the main existing known interventions and any known procedures for tapering? Are there no studies? This section claims 'the most obvious and obligatory intervention' is tapering. Can this judgment be made before the review is completed? (Also I believe tapering may not be necessary for fluoxetine owing to its long half life.) The sub-section, 'How the intervention might work' again seems imprecise to me and begins with a claim about the 'better life' of patients free from 'psychiatric medication' in general, without supporting evidence or a qualification of 'vast majority'. Similarly, the sub-section, 'Why it is important to do this review' says 'about half of the hundreds of millions of people who take antidepressants have become dependent on them.' I would prefer to see the exact figures. It also says 'It is evident that it would be beneficial for many patients' health to come off the drugs, particularly considering their long-term harms, which might involve irreversible brain damage including permanent sexual dysfunction.' Is it evident that these potential harms always outweigh the benefits? How common are these harms? In the Background section I should have hoped to see information about the interventions that are available for a variety of groups of patients using different antidepressants for different conditions in different settings and what uncertainties exist about them and their effectiveness. I am also interested to know whether this protocol arose from any form of priority setting involving consumers. The Background section projects enthusiasm about coming off antidepressants and psychiatric medication in general and places emphasis on the risk of side effects. I should like to see it clearly recognised that discontinuation is not safe in all cases and an indication of the risks and harms, supported by evidence. I believe it would be irresponsible not to do so when the subsequent review will be used to inform policy makers, health professionals, patients and carers. Patients need to be able to make an	symptoms are much the same for SSRIs as for benzodiazepines. It is highly relevant to quote Wunderink, see above. We have changed the wording, see above, and use severe, as suggested. We believe our list of withdrawal symptoms is very helpful for patients and doctors. People like to be informed. We do not guess, we are familiar with the literature, and it tells us that slow tapering is essential, also for fluoxetine. This will be clear in our review. We wrote: "The vast majority of patients who have managed to come off psychiatric drugs report that it has resulted in a better life overall." We now write: "Many patients…" (which everyone withdrawing patients can affirm). About half: We give several references to this in our review. We need not explain how common the harms are. See above about different drugs. We talk to patients every day, on the phone and via email, and one of us has withdrawn many patients. This experience is reflected in our protocol. It will be clear in our review what the harms are of withdrawing patients. The reviewer

	informed assessment of risks and benefits in order to make shared decisions. As it stands the protocol appears to me to be noticeably unbalanced.		wants patients to be able to make an informed assessment. We agree but why then does the reviewer recommend against informing patients of the possible withdrawal symptoms and brain damage caused by the drugs in order not to increase their anxiety?
	4. Objectives		
	Are the objectives specific and adequately justified?		
31.	**Editorial base – Lindsay Robertson (comment on v1):** The primary objective "to describe the current status of knowledge on how to withdraw antidepressant drugs safely" is too broad and vague. According to the Handbook, the primary objective of a Cochrane review should be to assess the effects of one or more healthcare interventions on stakeholder-important outcomes, both intended and unintended. The objective should be expressed in terms that relate to the population(s), intervention comparison(s) and, where appropriate to specify explicitly, the outcomes of interest.	Objective revised as suggested. **Ed Base check – Jess Hendon (comment on v2): Still too broad and vague.** **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree. It is unclear what the outcome is here – reducing withdrawal symptoms or coming off antidepressants.	The most important outcome for patients wanting to come off drugs is whether they succeeded coming off the drugs. Reducing withdrawal symptoms is a means to achieve this.
32.	**Steph Sampson (comment on v2):** This section reads differently than what has been argued up to this point. Assessing 'the effects of different interventions aimed at helping patients come off antidepressant drugs safely' is quite different to withdrawing patients who are dependent on antidepressants (addicts?). The stated objective seems fine, but it conflicts with the preceding argument.	We do not use the word addicts, so we cannot see there can be any problem. The reason why intervention/help is needed in these patients is withdrawal symptoms, which is what makes the patients dependent on taking them, which they say themselves in patient surveys (see above). **Ed Base check - Lindsay Robertson (comment on v3):** Suggest asking peer reviewers opinion on this. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Agree, although from my perspective, the arguments and assertions made in the Background do not provide adequate foundation for this protocol. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):**	We no longer use the term addiction. We believe our Background is very clear and if the editors disagree, please tell us exactly in what way. Our objective is also very clear: "To assess the effects of different interventions aimed at helping patients come off antidepressant drugs safely."

		Agree; again, speaks to need for clarity in the background and further clarity is then required in the objectives.	
33.	**Steph Sampson (comment on v2):** The different interventions listed here (tapering, psychotherapy, mindfulness, etc) would be better placed in the 'description of the intervention' sections, with a brief overview of 'how the intervention might work' for each stated.	Done, see protocol. **Ed Base check - Lindsay Robertson (comment on v3):** This has been done.	No comment needed.
34.	**Nuala Livingstone (comment on v3):** The objectives should include a more clearly defined populations and intervention of interest. (See MECIR Standard C1-4). Specifically, stating that the review is focused on 'different interventions' and 'patients coming off antidepressants' is not a clear definition of the population or intervention of interest.		See above.
35.	**Nuala Livingstone (comment on v3):** Authors state their objective is to "To assess the effects of different interventions aimed at helping patients come off antidepressant drugs safely", which implies the focus is on the process of withdrawal. However, this is inconsistent with the primary outcome of 'cessation'. Authors, should make one of the following two changes; a. If the focus of the review is on 'cessation', the objective should be updated to read "helping patients cease antidepressant use ~~come off antidepressant drugs safely~~". b. If the focus of the review is on the process of withdrawal, the objective can remain, but the primary outcome should be 'withdrawal symptoms', and not 'cessation'.		See above under points 31 and 32. We do not agree. This is not correct, see points 31 and 32.
	5. Selection Criteria		
36.	**Nuala Livingstone (comment on v3):** Authors are strongly encouraged to reconsider their eligibility criteria, to ensure it is clearly defined, unambiguous, and sufficiently narrow so that a meaningful answer can be obtained when studies are considered in aggregate. (See MECIR Standard C5-13). Key points for consideration are below.		See above. Our inclusion criteria should NOT be narrow.
	a. Types of Studies		
37.	**Editorial base – Lindsay Robertson (comment on v1):** Too vague. Are **cluster** and/or crossover trials to be included? What types of studies are excluded?	Revised, see protocol. **Ed Base check – Jess Hendon** See additional comments below	
38.	**Steph Sampson (comment on v2):** Are the authors only interested in studies that stop treatment completely? If so, this needs to be clearer, particularly in the 'Objectives'	See above. Interventions to help patients reduce/lower doses fall outside the scope of our review. We are interested in helping people come off antidepressant drugs completely and safely, and	See our reply in middle column. To lower the does is not our objective.

	section, which lists interventions that may not result in a complete stop to AD medications (e.g. tapering, dose reduction). The authors need to be clear what the endpoint is of RCTs sought – is it a complete stop to ADs, or an investigation of the various methods used to help reduce over time, whilst monitoring re-emergence/ withdrawal symptoms (which needs definition).	tapering plays a very important role in minimizing withdrawal symptoms. The primary endpoint of interest is – of course – complete cessation of antidepressant drugs. **Ed Base check - Lindsay Robertson (comment on v3):** To clarify this, it may be worth authors adding a sentence saying that interventions used to help reduce AD use will be excluded from the review? **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Agree – I think the authors have not adequately addressed the feedback in their protocol. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree – statements like this need to be added for clarity (and relevant to various aspects of the review), and the background needs to ensure that the reader has clarity about this. The way this section is presented suggests that authors will include all study types i.e. not just RCTs, but only randomised trials will be included in meta-analysis. Later it is suggested that only RCTs and comparative cohort studies will be included. Clarity is required.	As there are very few randomised trials, we wrote: "Studies of interest are those aimed at helping patients, through various interventions, come off any antidepressant drug completely. We will include randomised trials, also cluster randomised trials, and comparative cohort studies. All other types of studies on the subject will be excluded from the main analysis but might be described narratively in the Discussion section, if appropriate." Under Data Analysis we wrote: "We will include comparative cohort studies but will not meta-analyse them." There is no lack of clarity here.
	b. Types of Participants		
39.	**Editorial base – Lindsay Robertson (comment on v1):** Too vague. What about age, sex, setting, diagnosis of depression, types of antidepressants? Exclusion criteria? Need more information.	Revised, see protocol. **Ed Base check – Jess Hendon** See additional comments below	
40.	**Steph Sampson (comment on v2):** Could the authors provide more detail here? Also, authors may come across RCTs that look at withdrawal/ tapering for reasons other than patients wanting to come off the drugs, for example they may want to decrease their dosage/ help target their doses, etc.	See above. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Not sure what this means. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree: more detail required.	It seems that none of us, incl. the editors, understand what Sampson means. See also above.

41.	**Nuala Livingstone (comment on v3):** Authors have made a very strong argument in their background sections that clearly highlights the need for these interventions. However, authors also acknowledge in the Background section that "'People taking antidepressant drugs who wish to come off' is a very heterogeneous population". Rather than include every type of participants who 'wants to come off antidepressants', it may be of much greater benefit to decision makers and patients alike to conduct a well-defined robust systematic review that takes into account the heterogeneity of these patients and focuses only on certain types of participants within this population.		See above.
42.	**Question asked of consumer peer reviewer: *Do the proposed participants cover all relevant groups of people who might want to use this treatment? If not, who else would it be helpful to include or exclude?*** **Karen Morley (comment on v3):** "'People taking antidepressant drugs who wish to come off' is a very heterogeneous population." "We are interested in withdrawal irrespective of age, sex, setting, diagnosis of depression, types of antidepressants or the reason for wanting to come off." The data extraction section list includes diagnosis, duration of treatment, type of AD (but not individual ADs) and says these will be subject to subgroup analyses. As a consumer I should be interested in differences in findings related to age, sex, setting, diagnosis of depression and individual AD but this might make for an unwieldy review – I wonder if restricting its scope and making it more focussed would.		See above. We need to do a broad, not a narrow review in order to help people the best we can.
	c. Types of Interventions		
43.	**Editorial base – Lindsay Robertson (comment on v1):** Too vague. Factors to consider include different types of interventions, durations, dose reductions, comparator interventions etc. What interventions would be excluded?	Revised, see protocol. We cannot make too firm in- or exclusion criteria, as we are not planning a new trial but review what has been done. **Ed Base check – Jess Hendon** See additional comments below	
44.	**Steph Sampson (comment on v2):** As above – more detail on interventions needed.	See above. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Not sure what this means. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree; also, there is no detail about the comparisons.	See above. We write about Types of Interventions: "Any type of intervention aimed at helping patients withdraw from antidepressant drugs will be included. These may vary in terms of duration, speed, dose reductions, use of psychotherapy or other drugs, tapering support, medical assistance and degree of health care professional involvement. No types of interventions will be excluded, as long as the study measures antidepressant drug withdrawal."

45.	**Nuala Livingstone (comment on v3):** The 'Types of interventions' is not clearly defined. Authors should give specific examples of the different types of interventions and consider whether they are homogenous enough to pool together to produce a meaningful answer when studies are considered in aggregate.		See points 44 and 42.
46.	**Question asked of consumer peer reviewer:** ***Are the study interventions and comparisons/controls clearly described? Are the included interventions appropriate? If not, please explain.*** **Karen Morley (comment on v3):** Again, the scope seems very large to me, as any intervention is to be considered.		See above.
	d. Types of Outcome measures		
47.	**Editorial base (comment on v1):** More detail is required for each outcome. How will they be measured? What are withdrawal symptoms? Incidence and severity should be two separate outcomes.	Revised, see protocol. We cannot give too firm criteria, as we are not planning a new trial but review what has been done. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** All of this detail is required.	Primary outcomes is successful withdrawal, no detail required. We cannot detail secondary outcomes as we do not know how they have been described in the studies. As we wrote, see middle column, we are not planning a new trial where we can define things beforehand.
48.	**Steph Sampson (comment on v2):** 'Studies that meet the inclusion criteria will be included regardless of whether they report on the following outcomes.' – what's the justification here? It is standard practice that only studies that report the pre-specified outcomes will be included.	The editors should know that selective reporting is very common. Therefore, we include all studies of **Ed Base check - Lindsay Robertson (comment on v3):** I think the reviewer is pointing out that you cannot include a study in a systematic review if it does not measure any of the outcomes set in your protocol? This is not a case of pre-specified outcomes that are missing from the study report but outcomes that weren't defined and measured in the study at all. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** I agree with the authors here (this may be common practice in some groups, not in ours). **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** I agree also – ok to include studies on the basis of them meeting criteria re study type, participants and interventions even if they do not include outcomes specified in review. However, just to note that this does not mean that outcomes do not need to be defined a-priori.	We cannot imagine any withdrawal studies that do not mention whether people succeeded.

49.	**Steph Sampson (comment on v2):** What about 'successful dose reduction'? Not all RCTs will have participants reach a complete coming-off of the drugs, but a success may be found for some participants in achieving a lower dose, and consideration of the risks/ benefits of this seems sensible in a review like this.	"Successful dose reduction" is not an outcome in our review. It is very easy to reduce the dose, as virtually all patients are overdosed, so this is not of any interest to us. **Ed Base check - Lindsay Robertson (comment on v3):** If authors are only interested in complete withdrawal from ADs then I agree that successful dose reduction would not be an outcome of interest in this review. Suggest peer reviewer confirms this. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Agree. This needs clarifying in the protocol. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree	This is already very clear in our protocol (primary outcome).
50.	**Nuala Livingstone (comment on v3):** The primary outcome of "complete cessation of antidepressant drug use" should be more clearly defined. Specifically, it could be more feasible to focus on 'cessation by the end of the trial', as it may not be possible to know for certain if a participant has reached 'complete cessation' for life, as the participant may resume antidepressant use at a later date.		We cannot see how we could more clearly define a yes/no outcome. It is not a matter of complete cessation for life, as a patient might fall ill again.
51.	**Adam Todd (comment on v3):** Outcome measures: • Is the research team assessing if the antidepressants were restarted after they were stopped? This is a common problem in practice. • Will the outcome measures capture if an antidepressant was dose reduced, but not stopped? • Will the research team consider reporting the results according to antidepressant type? This may have important clinical implications for healthcare professionals who are involved in prescribing and reviewing antidepressants.		We will of course describe any such data. We are not interested in dose reductions. See above about various types of drugs.
52.	**Question asked of consumer peer reviewer:** ***Are the outcome measures (benefits and harms/side effects) the ones that are important to consumers, patients and the public? Can you highlight any other outcomes that are important to users of this review?*** **Karen Morley (comment on v3):** I am concerned that any potential harms of withdrawal in the longer term appear not to be given enough weight. Quality of Life and qualitative interviews of patients on their drug-free state are to be measured. Will longer term follow up be included? Though patient reported outcomes are of interest I should hope to see them alongside other quantitative measurements.		We will of course include anything of relevance in our review, even if it was not a prespecified outcome. We will of course include all studies of withdrawal, no matter what they mention about withdrawal symptoms.

	The primary outcome is described as 'complete cessation of drug use' and studies will be included regardless of whether they report on withdrawal symptoms. This is not what I expected from the title or objectives and relates to my question regarding the review title.		
	6. Search Strategy		
	Is there a thorough search for all relevant data using appropriate sources? Is the search unbiased, explicit and appropriately matched to the question?		
53.	**Editorial base – Lindsay Robertson (comment on v1):** Much more detail is required.	We believe our search strategy is adequate and sufficiently broad. One of us has done systematic reviews for over 30 years and is a very experienced searcher. **Ed Base check – Jess Hendon** See additional comments below more detail required.	
54.	**Steph Sampson (comment on v2):** This looks very sparse – consider have a search specialist construct search terms.	Our comment: Peter Gøtzsche has constructed literature searches for over 30 years, so no need for yet another search specialist here. Our search strategy utilizes the MeSH term system, wherein the MeSH term (antidepressants) captures all classes of antidepressant drugs (which is the scope of our review, as described above). It has never been demonstrated that it adds anything to search in multiple databases (we also scan reference lists). The term for "coming off antidepressant drugs" is trickier, as this may be called discontinuation, withdrawing, tapering, coming off, stopping, cessation and so on. We have added stop*, coming off* and cessat* so the search strategy now is: (antidepressants[MeSH Terms]) AND (withdraw* or taper* or discontinu* or stop* or coming off* or cessat*). **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Obviously we would expect a formal search is undertaken by our very experienced Information Specialist and for the authors to be transparent in accounting for their inclusion/exclusion decisions on this basis of this (and any other searches they wish to add as part of their wider search strategy). This should be clearly reflected in the associated tables and PRISMA flow chart).	The group wishes to help us with our searches, which we welcome.

55.	**Nuala Livingstone (comment on v3):** Searches must be as extensive as possible and include at a minimum CRG's Specialized Register (if it exists and was designed to support reviews in this way), CENTRAL, MEDLINE and Embase (See MECIR Standard C24).		See above.
56.	**Nuala Livingstone (comment on v3):** Authors state in the section 'Assessment of reporting biases' that they "will also search for unpublished studies", yet their current search strategic does not include any searches of trial registers or grey literature. (See MECIR Standard C27-28)		See above.
	7. Methods of the Review		
	Have the reviewers discussed all of the elements that should be covered in the methods section i.e. timeline for completion of the review, methods of locating and selecting trials, critical appraisal/quality assessment, methods of collection of data, analysis and presentation, improving and updating the review		
	General comments		
57.	**Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** The Methods section needs more work in accordance with MECIR standards.		The MECIR manual takes up 61 pages. As we cannot know what precisely you have in mind, we ask for specific advice, particularly as we feel we have written a protocol of a high standard.
	A - Selection of studies		
58.	**Nuala Livingstone (comment on v3):** It is preferable that two people would conduct the initial title/abstract screening of results to reduce both the risk of making mistakes and the possibility that selection is influenced by a single person's biases (See MECIR Standard C39).		Very often, just one person does the initial checking, and any doubts are checked by two people, which is what we write in the protocol.
	B - Data extraction and management		
59.	**Editorial base – Lindsay Robertson (comment on v1):** Much more detail is required. For example, what type of data will be extracted? Will you use a pre-piloted data extraction form? What happens if the two reviewers do not agree? Will you translate studies in a foreign language? What about missing data – will you contact the study authors for this?	Revised, see protocol.	
60.	**Steph Sampson (comment on v2):** Authors list 'type of antidepressant' info to be extracted from included studies, but provide no information on these up to now. Can the authors consider providing a	See above. We will of course mention the type of drugs in the studies we include. **Ed Base check - Lindsay Robertson (comment on v3):**	See above.

	more thorough overview of the different types of ADs, side-effect and withdrawal effect profiles, to make this information more meaningful at the data and analysis stage?	It would be helpful if there was a brief description of the AD classes and side-effects in the background rather than just talking about these in the reporting of the results. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agree as per above comments.	
61.	**Steph Sampson (comment on v2):** What scores will the authors use for data from continuous scales? Endpoint or change? A consideration of this is needed.	Endpoint scores if possible. If we need to combine change scores with endpoint scores, we will use the inverse variance method. (Added to protocol) **Ed Base check - Lindsay Robertson (comment on v3):** This has been added.	
62.	**Steph Sampson (comment on v2):** How do authors intend to handle skewed data?	Skewed data will be handled according to the Cochrane handbook for systematic reviews. (Added to protocol) **Ed Base check - Lindsay Robertson (comment on v3):** Suggest more information is added to this rather than just say according to the Handbook. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Agreed. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed. Also notice that some of this section discusses what might more rightly belong in the section on data synthesis. It also points to the need for more detail in the outcomes section (are there also dichotomous data that will be use?).	These methods are standard and are described in the Handbook. Cochrane reviews are, on average, very long, and much of them repeats what is written in the Handbook. We do not find this useful, but it is a minor issue, and we have added: "Section 9.4.5.3."
	C - Assessment of risk of bias in included studies		
63.	**Editorial base – Lindsay Robertson (comment on v1):** Too brief. Authors should state the different domains of bias and judgements on high, low or unclear risk of bias. Reference to the relevant section in the Handbook is also required. Also, two review authors should complete this independently and any disagreements should be resolved by discussion.	Revised, see protocol. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed	We have added, "independently."
64.	**Nuala Livingstone (comment on v3):** Authors must provide more detail on each domain of the Risk of Bias assessment. Authors must describe how the RoB tool will be implemented, and the criteria that will be used to assign study results to judgements of low risk, high risk and unclear risk of bias. (See MECIR Standard PR27).		This is standard and well described in the Handbook that we all need to adhere to. We write: "We will assess the risk of bias independently according to the Cochrane Handbook and external validity using the GRADE tool. We will use the 5 bias domains (selection bias, performance bias, detection

			bias, attrition bias and reporting bias) and judge whether there is a high, low or unclear risk of bias. The two review authors will do this independently and any disagreements will be resolved by discussion." We do not believe that Cochrane reviews should be more or less a copy of the Handbook. In research, it is very common, e.g. when analysing a chemical substance, to refer to a methods paper, and nothing more.
	D - Measures of treatment effect		
65.	**Editorial base – Lindsay Robertson (comment on v1):** More detail is required. What outcomes are dichotomous and what are continuous?	Revised, see protocol.	
66.	**Steph Sampson (comment on v2):** 'Continuous data will be analysed using the mean difference and standardised mean difference (SMD) as appropriate.' – Can the authors provide detail as to what situation would make either MD or SMD appropriate?	Yes, we can, but the editors can read about this themselves in the Cochrane handbook of systematic reviews under section 9.2.3.2 entitled "The standardized mean difference". SMD is used when the pooled studies are using different scales for the same measure (hence standardized mean difference), and MD is used when the studies are using the same scale (as there is no need to standardize data derived from the same scale, obviously). (Added to protocol) **Ed Base check - Lindsay Robertson (comment on v3):** Thanks for adding this explanation. It was for the benefit of the reader of the review, not the editors who are reviewing it. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed – and as per comment below this also highlights information that is missing from the protocol.	No comment needed.
67.	**Nuala Livingstone (comment on v3):** Authors refer to a plan to conduct a survival analysis for time to resolution of symptoms, but this was not listed as an outcome of interest.		We do not wish to do survival analyses. It is extremely unlikely that we will get access to individual patient data, and this type of analysis we believe was suggested by the editors. We have removed it from the protocol.

	E - Unit of analysis issues		
68.	**Steph Sampson (comment on v2):** More detail needed here – particularly in handling cluster RCTs and more specific statistics that would be used in various situations the authors may reasonably anticipate. What if there are multiple treatment arms? Would the authors combine similar groups (e.g. a three armed trial that may look at two different interventions aimed at tapering/ reducing doses versus maintenance treatment). More detail needed here.	We will analyse treatment arms separately, which we need not say, as this is implicit if there is no information about it. For cluster randomised trials, see the Cochrane Handbook. (Added to protocol) **Ed Base check - Lindsay Robertson (comment on v3):** I don't think stating "For cluster randomised trials, see the Cochrane Handbook" is enough. More information is required here. Of course refer to the handbook but you cannot expect the reader to find this when the chapter no is not even stated. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Agreed. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed. More detail is still required, no information has been added with regard to multiple treatment arms.	For cluster randomised trials, we have added: "section 16.3." For multiple treatment arms, we have added: "For multiple treatment arms, we will combine groups to create a single pair-wise comparison, see the Cochrane Handbook, section 16.5.4."
69.	**Nuala Livingstone (comment on v3):** For all planned analyses, authors must provide a clear and complete description of exactly how they will incorporate and analyse data. For example, stating "For cluster randomised trials, see Cochrane Handbook" is insufficient. (See MECIR Standard PR30).		See above.
	F - Dealing with missing data		
70.	**Editorial base – Lindsay Robertson (comment on v1):** Will you impute missing outcome data?	We cannot do this, as it would require access to individual patient data. **Ed Base check – Jess Hendon (comment on v2):** This is not correct please revisit	The Handbook mentions the difficulties and dangers with this and recommends statistical advice. Not relevant to revisit, as we do not say anything about individual patient data in the protocol. We wrote: "We will contact the original investigators to request missing data; if these data remain unavailable to us, we will try to perform intention to treat (ITT) analysis, in which it will be assumed that patients who dropped out did not come off the drug."
	G - Assessment of heterogeneity		
71.	**Editorial base – Lindsay Robertson (comment on v1):** Not enough detail. Please see Handbook for guidance on how to assess for heterogeneity	Revised, see protocol. **Ed Base check – Jess Hendon** See additional comments below	No comment needed.

72.	**Steph Sampson (comment on v2):** Can the authors provide more detail as to how they will handle data with high/ moderate levels of heterogeneity? How will this be defined? Suggest referring to the Cochrane Handbook for guidance on this.	If I-square exceeds 50%, we will explore reasons for heterogeneity, and use both random effect and a fixed effect model. (Added to protocol) **Ed Base check - Lindsay Robertson (comment on v3):** Authors have not included this sentence in this section. It appears under "Investigation of heterogeneity". I would suggest stating the different levels of heterogeneity as reported in the handbook. Also a specific reference, including chapter no, of the handbook should be given. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Agreed. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed. Again, refer to Handbook re different levels of heterogeneity, but also the other considerations with regard to heterogeneity.	We have added (in green): "Clinical and methodological differences between trials will be assessed before it is decided whether any meta-analysis would be feasible. Meta-analysis will only be performed when studies are sufficiently homogeneous in terms of outcomes, interventions and participants (see Cochrane Handbook, section 9.5.4). Heterogeneity between the trials will be assessed using I2 statistics, which describe the variation between trials in relation to the total variation."
	H - Assessment of reporting biases		
73.	**Editorial base – Lindsay Robertson (comment on v1):** Too vague. How will you look for evidence of publication bias? Simply stating "we will look" is not enough.	Revised, see protocol. **Ed Base check – Jess Hendon** See additional comments below	No comment needed.
	I - Data synthesis		
74.	**Editorial base – Lindsay Robertson (comment on v1):** Is this done in Review Manager? Need to reference the software. This section is too broad. How will studies of variable quality be dealt with in the meta-analyses? How will you deal with trials with more than two arms? Also need a description of the GRADE and how you will prepare summary of findings tables.	Revised, see protocol. **Ed Base check – Jess Hendon** See additional comments below still outstanding issues **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed. As above, some of this information has ended up in previous sections but should sit here.	See above.
75.	**Steph Sampson (comment on v2):** There is no discussion on how data for comparative cohort studies will be handled and included in the review. The same point for qualitative outcome measures. If there is a narrative/ thematic element planned, can the authors please provide an overview of how they will handle/ extract this data, and how they will include it in the analysis along with the quantitative evidence? What qualitative methods will be used? Is this a mixed methods review? Much more detail is needed here.	We will include comparative cohort studies but will not meta-analyse them. Other relevant studies will only be mentioned narratively, in our Discussion section. (Added to protocol) **Ed Base check - Lindsay Robertson (comment on v3):** Thanks for adding this sentence but more information is still required. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** Agreed. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):**	See above, it is already clear in the protocol.

		Agreed.	
76.	**Nuala Livingstone (comment on v3):** Authors plan to include comparative cohort studies but not meta-analyse them. Detailed methodological information on how information from these studies will be synthesised and presented in the review must be included in the methods section. (See MECIR Standard PR30).		We have now excluded these studies and will only, possibly, mention them, if any, in the Discussion.
77.	**Nuala Livingstone (comment on v3):** GRADE assessment- Authors must describe in detail the methods to be used to assess the quality of the body of evidence, with a more detailed description of the five GRADE considerations. (See MECIR Standard PR39)		We have added where in the Handbook this information is, as for the other technical details.
	J - Subgroup analysis and investigation of heterogeneity		
78.	**Editorial base – Lindsay Robertson (comment on v1):** Why are you not planning any subgroup analysis? What about age, sex, type of antidepressant, dose reduction? Have you considered these? Also need a more detailed account of how you're going to investigate heterogeneity.	There are not enough trials for such analyses but we have added a comment about this. **Ed Base check – Jess Hendon** See additional comments below this is not an acceptable response.	We have now written: "If the data permit this, we will do two subgroup analyses, dividing the studies into two groups of about equal size, those with drugs with a short and a long half-life, respectively. Active metabolites will count for this division." We have deleted the bit about heterogeneity.
79.	**Steph Sampson (comment on v2):** 'We do not plan any subgroup analyses because very few trials have been carried out.' – this isn't usually a justification at the protocol stage – usually authors pre-specify anticipated subgroup analysis based on data that can help answer the research question. Only when the data and analysis stage has been completed can the authors justify not performing a sensitivity analysis due to a lack of data/ reporting. Can the authors have a think about what subgroup analyses will be important/ significant to perform for this review?	Our comment: the editors go way over the top here. We know the area and there are so few studies that this point is not relevant. **Ed Base check - Lindsay Robertson (comment on v3):** Regardless of whether you know the area and that there are so few studies that subgroup analysis would not be possible, you should always pre-specify sub group analysis. This is common Cochrane practice. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** This is a critical point as (on the basis of the information provided) this review is likely to involve heterogeneous groups of patients and interventions. The plan for analyses needs to reflect this to ensure the interpretation of the evidence base reflects a comprehensive assessment of the available data. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed. This is about thinking through what might impact on the effects of interventions. I note the use of an arbitrary cut point re exploring heterogeneity, which is not recommended in the Handbook.	

80.	**Nuala Livingstone (comment on v3):** It is not an appropriate justification to state "we do not plan any subgroup analyses because very few trials have been carried out". Authors have previously established that the population of interest is very heterogenous, and therefore a planned exploration of potential effect modifiers would be expected. The presence of heterogeneity affects the extent to which generalizable conclusions can be formed. It is important to identify and explore heterogeneity in case there is sufficient information to explain it and offer new insights. (See MECIR Standard C63).		See just above.
	K - Sensitivity analysis		
81.	**Editorial base – Lindsay Robertson (comment on v1):** Why do you not plan sensitivity analyses? What about age range, dose range, quality of included studies?	There are not enough trials for such analyses but we have added a comment about this. **Ed Base check – Jess Hendon** See additional comments below this is not an acceptable response.	Thanks for this comment. We now write: "We will do a sensitivity analysis where only those studies are included where the patients took the initiative to getting their drug withdrawn. Such patients might be more motivated to endure any withdrawal symptoms, which might result in greater success rates."
82.	**Steph Sampson (comment on v2):** Do to authors not plan an SA? Can they please provide more detail here?	The editors go way over the top here, see just above. **Ed Base check - Lindsay Robertson (comment on v3):** It is standard Cochrane practice to plan a SA. Without pre-specified sub group and sensitivity analyses, the protocol will not be published. **Co-ordinating Editor Rachel Churchill (follow-up comment on v3):** See previous comments and associated MECIR standards. **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed	
83.	**Nuala Livingstone (comment on v3):** It is not an appropriate justification to state "we do not plan any sensitivity analyses because very few trials have been carried out". Authors should plan appropriate sensitivity analyses to assess the robustness of results, such as the impact of notable assumptions, imputed data, borderline decisions and studies at high risk of bias. (See MECIR Standard C71).		
	L – Summary of findings table		
84.	**Nuala Livingstone (comment on v3):** Authors must state which outcomes and comparisons will be included in the 'Summary of findings' table. (See MECIR Standard PR40) **Co-ordinating Editor Sarah Hetrick (follow-up comment on v3):** Agreed		We have added: "for the primary outcome."
	8. Other References		
85.	**Editorial base – Lindsay Robertson (comment on v1):** Many references in the list are not linked in the text.	Revised. **Ed Base check – Jess Hendon** NB will be rechecked at copyedit.	No response requested
86.	**Steph Sampson (comment on v2):**	Fixed. **Ed Base check – Jess Hendon**	No response requested

	The link to Wunderink 2013, Gibbons 2012, Rosenbaum 1998, Lucassen 2014 takes the reader to the Archie login page as opposed to its reference at the bottom of the page. Could be a tech glitch, but can the authors please check this with all refs.	NB will be rechecked at copyedit.	