National Institute for Health and Clinical Excellence

Anxiety (partial update)
Guideline Consultation Comments Table
20 July – 17 August 2010

No	Type	Stakeholder	Doc	Sec. No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
1	SH	Anxiety UK	Nice	1.2.1	12	As a point in principle, Anxiety UK very much welcomes the introduction of the 'stepped care model' in this guideline for GAD as it is felt that this aligns the guideline to the depression guideline which has formed the cornerstone of many new primary care mental health services, specifically Improving Access to Psychological Therapy (IAPT) services.	Thank you for your comment
2	SH	Anxiety UK	Nice	1.2.3	13	However, states that patient preference should guide choice of intervention within a 'step' it should generally not determine choice between steps (except 1 and 2). Anxiety UK disagrees with this statement as many patients have a good understanding of their needs, particularly those patients who may have accessed interventions previously at steps 1 and 2. This statement is also at odds with the principle of collaborative care, outlined earlier in the guideline under 'shared decision making'. We therefore feel strongly that patients should be involved in such decision making processes.	Thank you for your comment, but all reference to determining choice between steps was not in the consultation version of the guideline.
3	SH	Anxiety UK	Nice	1.2.7	15	Anxiety UK welcomes the addition to the guidelines of the insertion of a paragraph on the need for practitioners to be aware of those with GAD seeking reassurance around somatic symptoms. We do feel however that this guideline could be augmented by the production of a guideline on health anxiety as this is a common anxiety disorder, but one where there is significant overlap in terms of symptomatology with GAD.	Thank you for your comment. We agree that health anxiety is an important topic and would encourage you to submit this for consideration by the NICE topic selection panel.
4	SH	Anxiety UK	Nice	1.2.5	14	Anxiety UK welcomes the general focus in the guidelines on the need for early detection of GAD	Thank you for your comment.

						as our experience has been that many GAD sufferers do not receive a formal diagnosis of GAD for many years (having frequently being misdiagnosed). The new guidance on case identification and referral for common mental health disorders in primary care is to be welcomed and it is our feeling that this document will provide further clarification in this area.	
5	SH	Anxiety UK	Nice	General	3	We are concerned that only part of this guideline was updated (only the GAD aspect) as updated guidance is urgently needed in relation to the management and treatment of panic disorder and agoraphobia – it should be noted that we feel very strongly that the two conditions require separate guidance and should not be dealt with under the combined heading of 'panic and agoraphobia'.	Thank you for your comment. We were not asked by NICE to update the full clinical guideline for panic disorder and therefore were only able to partially update it.
6	SH	Anxiety UK	Nice	1.2.29	21	This section states 'do not offer an antipsychotic for the treatment of GAD in primary care'. Anxiety UK welcomes this statement as the charity has anecdotal evidence that the prescribing of antipsychotics (at sub-therapeutic doses) is widespread within primary care settings despite the potential for patients to develop adverse side-effects. The charity would however like to be advised of the communication strategy that NICE envisages being implemented in order to ensure that this element of the guidance is robustly adhered to by general practitioners.	Thanks for your comment. There is evidence that antipsychotics are being used in primary care, however, NICE are not directly responsible for implementation strategies for the guidelines. Nevertheless, this is likely to be an important aspect of dissemination and communicating with the NHS when we launch the guideline.
7	SH	Anxiety UK	Nice	1.1.4	12	states 'to inform people with GAD about local and national self help organisations and support in particular where they can talk to others with similar experiences'. Anxiety UK welcomes this statement and is particularly encouraged to see NICE's recognition of the value that user-led organisations have in the treatment and management of GAD and other anxiety related conditions. Peer support is extremely beneficial not least because it reduces the social isolation that many sufferers of GAD experience.	Thank you for your comment
8	SH	Anxiety UK	Nice	1.2.12	16	states that information about GAD should be given to patients. Anxiety UK very much	Thank you for your comments, we agree it is important for service users to be given relevant

						welcomes this statement as it is crucial that anxiety sufferers are given information that they can go away and read at their leisure. This is particularly so since many will be in a heightened state of anxiety when visiting their GP and therefore may be unable to assimilate what their GP advises. In being given an information resource on GAD (such as the GAD booklet that Anxiety UK has produced), patients then have the opportunity to read about their condition and to find out more about appropriate treatments. We would wish to point out however the importance of patients being given evidence based and credible literature on GAD.	and appropriate information.
9	SH	Anxiety UK	Nice	1.2.10	16	states 'if a person with GAD also has a comorbid depressive or other anxiety disorder, treat the primary disorder first (i.e. the one that is most severe and where it is likely that treatment will impact on overall functioning). Anxiety UK applauds NICE for making this statement as for many years it has been the case that anxiety has been seen as a secondary condition to depression rather than a primary diagnosis. This has caused impact not only at patient level but also within commissioning structures where depression has been the focus of attention to the detriment of anxiety. Anxiety disorders often require a very different treatment approach to depression therefore it is imperative that in cases where the primary presenting condition is anxiety, that anxiety is treated.	Thank you for your comment, we agree it is important to appropriately indentify and treat anxiety and hope that this guideline will encourage this.
10	SH	Anxiety UK	Nice	1.2.30	21	refers to the need for prescribers of SSRI antidepressants to make patients aware of activation syndrome associated with taking such medication. Anxiety UK welcomes this element of the guidelines as many of our clients have experienced severe difficulties and increased anxiety when taking SSRIs. Additionally many patients were never made aware that of the potential for their anxiety to be exacerbated during the first few weeks of taking an SSRI.	Thank you for your comment

11	SH	Anxiety UK	Nice	General	General	As a general point, Anxiety UK would wish to see physical exercise being endorsed within the guidelines despite the apparent lack of research evidence. Our experience has been that many GAD sufferers learn to manage their condition solely by changing their diet and undertaking physical exercise. The recommendation therefore in 4.4 for further research is much welcomed.	Thank you for your comment. We are unable to recommend interventions that do not have an evidence base.
12	SH	Anxiety UK	Nice	1.2.40	23	Whilst the guideline states that a referral to secondary care/step 4 should be considered if the person with GAD has severe anxiety with marked functional impairment, Anxiety UK would have concerns about the reality of such individuals being seen at this level as the charity's experience is that very few people meet the stringent criteria set by services at this level. It is however encouraging to see the additional bullet point under this section which states that a person should be 'considered' for 'step 4' services in the event that an inadequate response to step 3 interventions has been evident. The word 'considered' however is probably too weak and should be replaced with something stronger. In a similar vein, Anxiety UK welcomes the research recommendation 4.6 as experience shows that collaborative care models enhance treatment outcomes however the divide between services operating at primary and secondary care level often acts as a barrier to this.	Thank you for your comment. This recommendation regarding specialist interventions at Step 4 has been changed so as to clarify that they are not only delivered in secondary care services; they may be delivered in different service configurations and settings. However, the word 'consider' reflects the strength of the evidence and therefore we have not altered this wording. Thank you, we agree this is an important area for research.
13	SH	Anxiety UK	Nice	1.2.11	16	This section although welcomed, does not in our opinion pay sufficient attention to the growing problem of the self-management of mental health conditions such as GAD by individuals with substances such as alcohol and/or illicit drugs. Anxiety UK's experience is that many individuals self-manage GAD with alcohol and that this effectively forms part of their 'coping' strategy. As such we feel that individuals presenting with GAD should be routinely asked about their alcohol intake/drug intake in order that a comprehensive	Thank you for your comment. The management of people with GAD who misuse drug or alcohol has been covered in NICE guidance 1.2.8. We acknowledge that some people with GAD and comorbid harmful or dependent alcohol misuse will go on to need consecutive or concurrent treatment for GAD.

						overview of the presenting problem is obtained. Without doing this, treatment programmes may be at risk of failing/will not stand the best chance of success. It seems as if the issue of 'self management of GAD by the use of alcohol/drugs' has been somewhat overlooked with instead there being emphasis on the need not to turn individuals away from services if it is detected that they use alcohol etc.	
14	SH	Anxiety UK	Nice	4.5	43	Anxiety UK welcomes NICE's recognition of the need for further research in the field of the treatment of GAD via complementary medicine, in particular the use of chamomile. Many of Anxiety UK's clients use and have used such substances as relaxation aids yet to date there appears to be insufficient data to support an evidence base in this area. Further research in this area would therefore be much welcomed.	Thank your for your comment
15	SH	Anxiety UK	Nice	4.3	41	Anxiety UK welcomes the research recommendation 4.3 around ascertaining the clinical and cost effectiveness of computerised CBT (CCBT) versus CBT for the treatment of GAD. The charity's experience is that many individuals experiencing GAD benefit from being given access to CCBT so long as they are provided with support throughout their accessing of the CCBT package. Indeed CCBT services often present a non-stigmatising and accessible way for those experiencing anxiety to access services.	Thank you for your comment.
16	SH	Association for Family Therapy and Systemic Practice	All	General	General	AFT, The Association for Family Therapy and Systemic Practice (UK) recognises that families and carers are more acknowledged in this Update, but without enough recognition of the role of close relationships in either triggering anxiety, having to deal with the impact of anxiety, or having a role in recovery if they are involved in treatments. Descriptions of how these can be address by systemic couple and family therapy can be found on the AFT website: www.aft.org.uk	The role of families and carers has been covered in recommendations 4.5.6.3, 5.3.4.2 and 5.3.4.3. We agree that there is scope for further research into family therapy along with all psychological therapies. However we followed the criteria for selecting high-priority research recommendation process set out in the NICE guideline development manual. Using this process, family therapy did not come out as being of the highest priority.

17	SH	Association for Family Therapy and Systemic Practice	All	General	General	Suggest that Therapeutic Alliance is acknowledged as important for people with anxiety, and Therapeutic Competence (see *The Competencies required to deliver effective Systemic Therapies*. Pilling, S., Roth, A.D. & Stratton, P. www.ucl.ac.uk/clinical-psychology/CORE/systemic_framework.htm~map . The draft consultation for Alcohol dependence and Harmful Use includes this topic, which provides a recognition of the skills and the value of different psychotherapies which people with anxiety will be using, although there may not be an evidence base that fits with NICE criteria.	Thank you for drawing attention to this. We do acknowledge the importance of therapeutic alliance. The recommendations on the delivery of high intensity interventions include that they should be delivered by trained and competent practitioners. As you set out, competence frameworks include establishment and maintenance of the therapeutic alliance as a core competence. Our introductory section on person-centred care also sets out the importance of all care and treatment being based on a collaborative therapeutic relationship.
18	SH	Association for Family Therapy and Systemic Practice	NICE	1.2	10	Stepped Care treatments should include addressing the relationship and family issues where appropriate eg and the impact of anxiety of relationships, work and on functioning, as well as how anxiety can be triggered off by events, conflicts, or trauma, often involving people who the person is attached to, as described in the personal stories.	Thank you for your comment. The treatments reviewed which are the subject of the recommendations of this guideline did not explicitly address these issues, so there is not a specific recommendation to address these. However, in so far as trained and competent practitioners of the recommended treatments in this guideline address these issues where relevant in the course of provision of these treatments, this is covered under the recommendations regarding practitioners being trained and competent (see 1.2.18, 1.2.19).
19	SH	Association for Family Therapy and Systemic Practice	NICE	1.2.42	10	[Also FULL 5.4.3.7 page 97] Suggest that couple /family interventions are included in Step 4 because of the impact of anxiety, which may have been triggered off by an event that affected other family members too, as well as the role of partners / families in supporting people with anxiety. *'Systemic interventions create a context within which families can support recovery and a forum within which family interaction patterns and belief systems that often inadvertently maintain anxiety disorders can be transformed'* p54 Carr, A.	Thank you for drawing attention to this. We have noted your comment, but the suggested intervention focused on children, which is outside the scope of this guideline.

						(2009):The effectiveness of family therapy and systemic interventions for adult focused problems. Journal of Family Therapy. 31.1.46-74.	
20	SH	Association for Family Therapy and Systemic Practice	NICE	1.2.8	12 -13	Given the evidence for the links between anxiety and alcohol problems, and the strong cost effectiveness or couples therapy recommended by *Alcohol dependence and harmful use* draft guideline, systemic therapies have a valuable role. If the evidence doesn't fit with NICE criteria, then suggest that there is a research recommendation to evaluate the value of couples therapy and anxiety.	Thank you for your comment. The evidence does not fit with our methodology criteria. Couples therapy has been considered for research recommendation, but the research recommendations in our guidance are prioritised for the reasons explained in the chapter.
21	SH	Association for Family Therapy and Systemic Practice	FULL	4.2 4.3	51 66	The personal stories highlight the role of personal experiences, families, and events in families that trigger anxiety – and the value of psychotherapeutic relationships. People who seek couple and family therapy don't always identify anxiety as the focus, and may prefer to address the relationship issues. One description of couple therapy with anxiety can be found: Baucom, Stanton & Epstein (2003): *Anxiety Disorders*. In Snyder & Whisman (eds): Treating Difficult Couples. Helping Clients with Coexisting Mental and Relationship Disorders. Guilford Press. New York.	Thank you for your comment and for the reference. However as Baucom *et al.* did not specifically cover patient experience we did not include it in our review.
22	SH	Association for Family Therapy and Systemic Practice	FULL	3.6.2	47	A study on the costs of different treatments, including the costing of different professionals involved, shows the economic value of Family and Marital Therapists for different diagnoses in USA. Anxiety is included in the diagnoses. Russel Crane, D. & Payne, S.H.,(2009): *Individual versus Family Therapy in Managed Care: Comparing the Costs of Treatment by Mental Health Professions*. Journal of Marital and Family therapy.	Thank you for this information. The paper provides costings of different therapists in the USA. Unfortunately, such costings are not relevant to the UK setting and therefore to this guideline. Moreover, this guideline does not examine the difference in costs across different professions; neither makes specific recommendations on which type of health professional should deliver a particular psychological intervention. Rather, the economic analyses undertaken in this guideline estimated the costs to the NHS associated with provision of clinically effective psychological interventions, as demonstrated in the guideline systematic review of clinical literature.

23	SH	Association of Psychoanalytic Psychotherapy in the NHS and Tavistock & Portman NHS Foundation Trust[1]	Full	General	General	[Also NICE version page 22] The draft guidance is a partial systematic review of the evidence for medication and CBT for GAD, and low-intensity computerised CBT for panic disorder. The draft guideline should make it clear, however, that it is not a systematic review of psychosocial treatments for panic disorder and / or GAD, and that its partial recommendations are restricted in scope, therefore, as the guideline development group did not follow a systematic process for psychosocial treatments other than CBT.	Thank you for your comment. The remit for this guideline was to update both pharmacological and psychological interventions for GAD. We have systematically searched all psychosocial treatments for GAD and our review includes studies of CBT, psychodynamic therapies and counselling. In addition, the remit was to also update cCBT for panic, as part of the technology appraisal update (NICE, 2006 TA97). We were not asked by NICE to update the full clinical guideline for panic disorder.
24	SH	Association of Psychoanalytic Psychotherapy in the NHS and Tavistock & Portman NHS Foundation Trust	Full	General	General	[Also NICE version page 22] These comments are restricted therefore, to general points about the process that has not been followed for a systematic review of psychosocial treatments, and the impact this has had, perforce, on invalidating the draft as it stands as a systematic review that could be published by NICE as a clinical guideline. We are unclear why the usual process, as stipulated in the NICE guidance on methodology, has not been followed in this instance. We will take this up with NICE directly, as the impact on implementation within services is potentially, otherwise, very serious and damaging if this draft is published as a partial clinical guideline update.	Thank you for your comment. The anxiety update scope was not consulted on as per the methodology outlined in the NICE guidelines manual (2009: see chapter 14). If a partial update does not look at any new areas for review, the manual states that the scope does not need to go out for consultation.
25	SH	Association of Psychoanalytic Psychotherapy in the NHS and Tavistock & Portman NHS Foundation Trust	Full	General	General	[Also NICE version page 22] In order to ascertain the scope of the guideline the relevant stakeholders should be consulted. This did not happen. The draft scope was not circulated and a final scope was agreed that did not provide any valid rationale from which an update of the 2004 guideline could be undertaken through a systematic review process.	Thank you for your comment. The anxiety update scope was not consulted on as per the methodology outlined in the NICE guidelines manual (2009: see chapter 14). If a partial update does not look at any new areas for review, the manual states that the scope does not need to go out for consultation.

[1] This was a joint submission by four organisations, although only two of these were registered stakeholders

26	SH	Association of Psychoanalytic Psychotherapy in the NHS and Tavistock & Portman NHS Foundation Trust	Full	General	General	[Also NICE version page 22] In order to ensure the relevant evidence is reviewed thoroughly and the relevant criteria are applied to select and analyse the evidence, an expert group needs to be formed from the range of relevant experts. This did not happen. The guideline development group contained no experts in dynamic therapies who would have been necessary to consult for a review of the evidence for GAD / panic disorder for psychosocial therapies.	Thank you for your comments, but we disagree about the opportunity for involvement of a range of relevant experts. Vacancies for GDG positions are posted on the NICE website. They may also appear on the website of the NCC and/or the Royal College or professional body that hosts the NCC, and in other appropriate places identified by the NCC. Furthermore, NICE informs registered stakeholder organisations about the advertisement. Finally, the consultation period provides further opportunity for relevant experts to review the evidence and provide feedback on the guideline.
27	SH	Association of Psychoanalytic Psychotherapy in the NHS and Tavistock & Portman NHS Foundation Trust	Full	General	General	[Also NICE version page 22] In order to ensure the experts have developed draft recommendations based on a thorough, systematic review of the evidence, applying the right criteria, the relevant external expert reviewers are needed to check the review. This did not happen. The guideline development group did not consult with any external experts in dynamic therapies for GAD and / or panic disorder to ensure the evidence had been thoroughly and systematically reviewed and the right criteria applied.	Thank you for your comments. We do have a number of registered stakeholders with expertise in this area. Given the evidence of psychodynamic therapies is quite small, the current stakeholders' expertise would have covered any questions in the review process. Furthermore, the consultation period provides further opportunity for relevant experts to review the evidence and provide feedback on the guideline.
28	SH	Association of Psychoanalytic Psychotherapy in the NHS and Tavistock & Portman NHS Foundation Trust	Full	General	General	[Also NICE version page 22] In order to undertake economic modelling based on a thorough and systematic review of the relevant evidence for efficacy and cost, the relevant psychosocial treatments for an update to the 2004 guidance need to be considered. This did not happen. Based only on a partial review of efficacy of medication, CBT treatments, and their costs, it is not possible to construct an economic model that will identify the cost-effective psychosocial treatment options for GAD and / or panic disorder. For this reason, we would not support publication of this partial update / review.	The economic analyses undertaken for this guideline considered all low-intensity psychological interventions, high-intensity psychological interventions and pharmacological treatments for GAD that were found to have an acceptable harm-to-benefit ratio in the guideline systematic review of clinical evidence. We did undertake a full (not partial) review of efficacy of the above interventions. We have systematically searched all psychosocial treatments and reviewed CBT, psychodynamic therapies and counselling. The search methods and inclusion criteria for studies evaluating treatments for

							GAD have been reported in Chapter 3, with more details given in the respective evidence chapters of the full guideline. Regarding Panic Disorder, the guideline only updated the NICE TA on cCBT for panic disorder. Consequently, no other treatments for panic disorder (except cCBT) were evaluated in terms of their clinical and cost effectiveness.
29	SH	British Association for Counselling and Psychotherapy	Full	General	General	BACP thanks NICE for the opportunity to comment on this partial update.	Thank you for your comment.
30	SH	British Association for Counselling and Psychotherapy	Full	7	152 -197	BACP acknowledges that John Cape is the Chair of the guideline development group, but would like to reference his article 'Brief psychological therapies for anxiety and depression in primary care: meta-analysis and meta-regression'. The article concludes that brief CBT, counselling and problem solving therapy are effective treatments for anxiety and depression in primary care.	Thank you for the suggested reference. However, this guideline focused on treatments for GAD and panic disorder. In the Cape *et al.,* 2010 review, the only studies specifically of anxiety populations, including GAD and panic disorder, were of CBT; there were no studies in that review of counselling or problem solving therapy for anxiety disorders
31	SH	British Association for Counselling and Psychotherapy	Full	7	152 -197	Two empirical studies have been conducted at Penn State University on an integrative treatment for GAD. The treatment was aimed at improving the efficacy of CBT by adding to this approach, techniques from humanistic, interpersonal, and psychodynamic treatments. The first study (Newman et al., 2008) was an open trial, which provided preliminary support for the integrative treatment, by showing pre-post effect sizes that compare favorably to those obtained in previous studies on CBT. The second study (Newman et al., submitted for publication) was a randomised clinical trial, comparing the integrative treatment with CBT. The results, however, show that the integrative	Thank you for your comment and for bringing these two studies to our attention. The first study referred to (Newman, 2008) has not been included as it does not meet our inclusion criteria (i.e. it is an open study and not an RCT). The second study is not yet published and thus cannot be included in the current guideline. The point about identifying predictors of types individuals with GAD for whom current CBT interventions may not be adequate and identifying interventions which might improve outcomes for them is well made, and future research in this area will hopefully contribute to future guideline updates.

						treatment did not lead to significantly better outcomes on most of the outcome measures. As noted in the discussion of Newman et al (submitted for publication), an important next step for the team is to conduct analyses to identify individuals with GAD that may benefit from adding to CBT interventions aimed at addressing emotional, interpersonal, and developmental issues that have been linked with the etiology and maintenance of this problem. Since CBT is an effective treatment for at least 50% of clients who receive it, it stands to reason that not all of them will need more than what this treatment already offers but some others may. The question is not what is the best (or only acceptable) treatment, but what works more for whom. Reference: Newman, M. G., Castonguay, L. G., Borkovec, T. D., Fisher, A. J., and Nordberg, S. S. (2008). An open trial of integrative therapy for generalized anxiety disorder. *Psychotherapy Theory, Research, Practice, Training* Vol. 45, No 2, 135-147.	
32	SH	CCBT Ltd.	NICE	General	General	[Also pages 4-5 NICE version] Using just DSM-IV and ignoring ICD-10 diagnoses omits ICD-10 F40.0 `Agoraphobia' without panic disorder for which studies show the efficacy of exposure therapy. Crucial because agoraphobic avoidance is the chief cause of disability in panic disorder.	Thank you for this comment. In line with the previous anxiety guideline and other NICE guidelines for anxiety disorders and depression (NICE, 2004; 2009b) we have used DSM-IV, rather than ICD-10 to define the diagnosis of GAD, because the evidence base for treatments nearly always uses DSM-IV. Also, agoraphobia is beyond the scope of this guideline.
33	SH	CCBT Ltd.	NICE	1.3 & 1.4	22 -34	Important to stress that agoraphobic avoidance increases panic and disability & improves with exposure therapy.	Thank you for your comment. All text shaded grey has not been updated by this guideline and therefore is not being consulted on.
34	SH	CCBT Ltd.	NICE	1.4.7	25 -26	Important to use RP Swinson's RCT finding in an A&E (Am J Psychiat 1992, 149:944-946) that a few minutes of exposure advice reduced both panic and agoraphobia more than relaxation	Thank you for your comment. All text shaded grey has not been updated by this guideline and therefore is not being consulted on.

						advice up to 3 months follow up.	
35	SH	CCBT Ltd.	NICE	1.4.15 1.4.16 1.4.18	27 27 28	Only 1 - 2 hours of therapist support is needed if allow panic disorder patients to self-treat using FearFighter CCBT.	Thank you for your comment. All text shaded grey has not been updated by this guideline and therefore is not being consulted on.
36	SH	CCBT Ltd.	NICE	1.4.37	31	Can add that FearFighter is COST-effective (McCrone et al CBT 2009, 34, 1-9 DOI: 10.1080/16506070802561074.	Thank you for your comment. The recommendation has been removed from the guideline, as the evidence relating to FearFighter does not meet the inclusion criteria of this guideline.
37	SH	CCBT Ltd.	NICE	1.4.41	32	Most panic disorder can be assessed within 30 minutes.	Thank you for your comment. All text shaded grey has not been updated by this guideline and therefore is not being consulted on.
38	SH	CCBT Ltd.	NICE	1.4.49	34	Also need to assess agoraphobic avoidance e.g. with Fear Questionnaire.	Thank you for your comment. All text shaded grey has not been updated by this guideline and therefore is not being consulted on.
39	SH	CCBT Ltd.	FULL	6.1	106	Training to use self help materials has been an issue for even experienced therapists (Cognitive Behaviour Therapy Self-Help: Who Does it Help and What are its Drawbacks? Melanie MacLeod, Rebeca Martinez and Chris Williams *Behavioural and Cognitive Psychotherapy*, 2009, 37, 61–72) where lack of training leads to recommending self help much less. cCBT should be an integral part of curriculums designed to train low intensity therapists.	Thank you for your comment. We agree clinicians should be trained in delivering low intensity interventions. This has been covered in our NICE recommendations Step 2 of the stepped care model.
40	SH	CCBT Ltd.	FULL	9.1.7	343 -344	NICE's TABLE 81 mistakenly claims in its bottom line that the Completion rate for both studies was unclear. In fact, the Marks et al (2004) report shows: -in its FIGURE 1 (CONSORT diagram), that Completion rate at the end of treatment for each group was for: FearFighter 21/37 [57%], Clinician 29/39 [74%], Relaxation 16/17 [94%], -in its ABSTRACT and/or text, that: i) dropouts (i.e. non-completers) occurred significantly more often in the two self-exposure groups combined (computer [*FearFighter*]-guided + entirely Clinician-guided) than in the psychological-placebo control group having computer-guided self-relaxation. The highest completion rate was in the ineffective	Thank you for your comment. The Fear Fighter studies have now been removed from the guideline as our guideline does not cover phobia population.

						psychological-placebo control group. ii) though there more dropouts (non completers) in the *FearFighter*-guided group than in the entirely Clinician-guided group, this difference was not statistically different (p=0.13). iii) at week 0 pre-treatment, the eventual completers had not differed significantly from the eventual non-completers on any demographic or clinical variable or or motivation. iv) reasons for dropping out (noncompletion) were similar across the three groups. The Schneider et al (2005) report also shows the Completion rate for each group: i) in its FIGURE 1 (CONSORT diagram), Completion rate at the end of treatment was very similar across the 2 groups - for: internet-FearFighter 33/43 (77%), internet-Managing Relaxation control 15/21 (71%). ii) in its text, that the reasons for dropping out (noncompletion) were similar across the two groups iii) at week 0 pretreatment, the eventual non completers had a more severe main phobia score than the eventual completers.	
41	SH	College of Mental Health Pharmacy	NICE	1.2	12	Under the heading *"Assessment and education"* there is no mention of identification of the presence or lack of a trigger or precipitant of the anxiety symptoms nor time course. They are covered in the introduction on page 4 and Appendix C but they could also be helpful here.	Thank you for your comment. This section is not intended to cover all issues to do with assessment and diagnosis. Appendix C has been included in order that there is a practitioner oriented summary of the key diagnostic and assessment issues.
42	SH	College of Mental Health Pharmacy	NICE	1.2.22	16	*"If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). Offer Sertraline first because it is the most cost-effective drug. Monitor the person carefully for adverse reactions"* We are concerned about this recommendation for a number of reasons*:* 1. The recommendation of an unlicensed product that has not been formally assessed for efficacy, safety or tolerability	Thank you for your comments. We do not believe that the available clinical evidence (2 RCTs with 706 participants of 12 weeks duration each) is insufficient to demonstrate sertraline's safety, tolerability and effectiveness in people with GAD. Sertraline was found to be associated with the lowest risk for discontinuation due to side effects (demonstrated in both classical and network meta-analysis) and with one of the highest

						in GAD is a cause for concern. 2. Additionally GAD is a long term chronic condition and there are no long term studies of sertraline in GAD to support its continued use in the condition. (1.2.32 (page 19 NICE version) recommends treatment for at least a year) There are data beyond six months for both venlafaxine and escitalopram 3. This recommendation is also in contradiction to guidance published by the GMC (Sept.2008), the RCPsych (Jan 2007), and the MHRA (April 2009). Like the other organizations , the MHRA states that *Before prescribing a medicine off-label,* • *be satisfied that such use would better serve the patient's needs than an appropriately licensed alternative* • *be satisfied that there is a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy* • *give patients, or those authorising treatment on their behalf, sufficient information about the proposed treatment, including known serious or common adverse reactions, to enable them to make an informed decision* • *explain the reasons for prescribing a medicine off-label where there is little evidence to support its use* 4.We do not believe that the evidence suggests that sertraline as a first line medicine would serve the patient's needs better than an "appropriately licensed alternative" of which there are two SSRIs suitable for first line use as well as two SNRIs and pregabalin for later use. 5. It would appear that this recommendation is made solely on the basis of cost, which in our opinion is unacceptable and inconsistent with a	response rates across drugs. The guideline economic analysis (which took into account the uncertainty underlying the clinical data) demonstrated that sertraline had 70% probability of being the most cost-effective drug at the NICE cost effectiveness threshold of £20,000/QALY. This result was based on a combination of clinical and cost data. Our recommendation was not 'made solely on the basis of cost'. Please note that paroxetine was the second least expensive option, but its ranking was very low in terms of cost-effectiveness due to respective clinical data (high discontinuation rates and low response rates relative to other drugs). Regarding the economic analysis undertaken in the depression guideline, this used data from a published network meta-analysis; the full results of the network meta-analysis were not available and therefore the uncertainty underlying those data was not possible to incorporate and consider in the economic analysis. This was potentially what influenced the recommendation. Nevertheless, we have slightly changed the recommendation in the light of your comments ('offer sertraline' has been replaced by 'consider offering sertraline'). We have also removed the bullet point that asks prescribers to take into account UK marketing authorisation for use in GAD.

						previous NICE clinical guideline where NICE performed a similar economic evaluation which showed sertraline, which is licensed for depression, to be more cost effective than all other SSRIs in the management of moderate and severe depression (CG90) but failed to make this the basis of a recommendation. 6. Prescribers are required to explain to patients the reason for prescribing "off label" and to get their consent which must be documented. This is a cumbersome and intrusive process and is likely to increase anxiety levels in someone already significantly disabled by GAD. 7. Recommendation 1.2.22 is inconsistent with recommendation 1.2.1 (page 10 NICE version) which states *"Offer the least intrusive and most effective intervention first"* It is also inconsistent with the statement in 1.2.23 (page 16 NICE version) which urges prescribers to take into account "*UK marketing authorization for use in GAD"* - if sertraline is ineffective.	
43	SH	College of Mental Health Pharmacy	NICE	1.2.24	17	*"If the person cannot tolerate SSRIs offer pregabalin rather than an SNRI "* *There is one generic SNRI but no generic pregabalin. Both are licensed for GAD but this recommendation supports the most expensive option despite it not being supported by any economic analysis. Again this inconsistent especially since there is no compelling evidence of increased efficacy of pregabalin over other licensed products.* *The use of a second SSRI, as tolerability/acceptability differ, or venlafaxine would be a more appropriate recommendation here based on efficacy and cost.*	Thank you for your comment. We have amended the recommendation in the light of your comment. However, we believe that pregabalin should be offered as a last pharmacological treatment option if SSRIs or SNRIs are not tolerated. Pregabalin was found to be the least cost-effective drug but was still more cost-effective than placebo.
44	SH	College of Mental Health Pharmacy	FULL	8.2.3	202	Is the stated use of DSM-IIIR a mis-print here?	No the stated inclusion of studies using either DSM-IIIR or DSM-IV was not a misprint. The GDG concluded that while there is substantial

							difference in diagnostic criteria used in DSMIII and earlier criteria when compared to current DSM-IV criteria this was not the case for DSM-IIIR
45	SH	College of Mental Health Pharmacy	NICE FULL NICE FULL	1.2.22 1.2.24	16 203 17 215	*"If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). Offer Sertraline first because it is the most cost-effective drug. Monitor the person carefully for adverse reactions"* Compared to placebo: *Only 2 RCTs (n=706) for sertraline versus placebo were considered by the GDG compared to 6 (n=2136) and 8 (n=2784) for the other SSRIs licensed for GAD – escitalopram and paroxetine respectively while 12 (n=3470) were considered for venlafaxine the licensed SNRI. All of the SSRI studies were rate as "High" by the GDG. The efficacy outcomes and harms were similar across all drugs. Discontinuation due to adverse events was least with escitaloptam.* *8 RCTs (n=2145) were considered for pregabalin – there was moderate benefit with small effect size and adverse effect whilst different were significant* **On the basis of the very limited data reviewed and lack of license we feel that sertraline should not be the first line recommendation for GAD. Instead one of the licensed SSRIs should be considered before the patient is put at risk of non-response or adverse effects of a medicine not licensed for GAD and for which there is no long term data in this condition.**	We do not believe that the available clinical evidence (2 RCTs with 706 participants, with duration 12 weeks each) is insufficient to demonstrate sertraline's safety and effectiveness in people with GAD. Sertraline was found to be associated with the lowest risk for discontinuation due to side effects (demonstrated in both classical and network meta-analysis) and with one of the highest response rates across drugs. The guideline economic analysis (which took into account the uncertainty underlying the clinical data) demonstrated that sertraline had 70% probability of being the most cost-effective drug at the NICE cost effectiveness threshold of £20,000/QALY. Nevertheless, we have slightly changed the recommendation in the light of your comments ('offer sertraline' has been replaced by 'consider offering sertraline').
46	SH	College of Mental Health Pharmacy	FULL	8.3	236	Head to head studies: *Escitalopram was found to be statistically more efficacious (HAM-A score) than paroxtine, in addition there was a 40% reduction in risk of non response with escitalopram compared to paroxetine which also caused mare disconmtinuation due to side-effects.* *No differences in efficacy were found between venlafaxine and escitalopram but there was a*	We do not believe that the available clinical evidence (2 RCTs with 706 participants of 12 weeks duration each) is insufficient to demonstrate sertraline's safety and effectiveness in people with GAD. Sertraline was found to be associated with the lowest risk for discontinuation due to side effects (demonstrated in both classical and network meta-analysis) and with one of the highest

						greater risk of iscontinuation with venlafaxine. *There were no statistically significant differences found between sertraline and paroxetine on any outcome* **On the basis of the very limited data reviewed and lack of license we feel that sertraline should not be the first line recommendation for GAD. Instead one of the licensed SSRIs should be considered before the patient is put at risk of non-response or adverse effects by using a medicine not licensed for GAD and for which there is no long term data in this condition.**	response rates across drugs. The guideline economic analysis (which took into account the uncertainty underlying the clinical data) demonstrated that sertraline had 70% probability of being the most cost-effective drug at the NICE cost effectiveness threshold of £20,000/QALY. Nevertheless, we have slightly changed the recommendation in the light of your comments ('offer sertraline' has been replaced by 'consider offering sertraline').
47	SH	College of Mental Health Pharmacy	All	General	General	In a previous guideline, NICE (CG38) states that it *"recommends some drugs for indications for which they do not have UK marketing authorisation at the date of publication, if they are already in use in the NHS for that indication, and there is evidence to support that use."* In the case of Sertraline for GAD we do not believe this to be the case	Thank you for your comment. We are not basing the current recommendation on the criteria laid out in CG38, but rather on the efficacy and cost effectiveness data on sertraline that were available. Sertraline is commonly used in clinical practice for the treatment of depression and mixed depression and anxiety. We recognise the fact that it may not be used commonly for the treatment of diagnosed GAD, but we believe this is because primary care doctors in the UK do not usually define patients as having GAD. The use of sertraline for GAD is supported by the clinical and economic evidence presented in the guideline.
48	SH	College of Mental Health Pharmacy	All	General	General	The CMHP supports the concept of evidence based medicine and in doing so regrets the fact that since 2006 NICE has chosen not to support the recommendations in it clinical guidelines with evidence gradings. unlike other National Guidance e.g.that from the BAP. This in our opinion reduces the utility of NICE guidelines.	Thank you for your comment, we agree with the judgement of NICE that grading evidence purely on the basis of study design can be misleading. It is our judgement that the GRADE approach provides a much more comprehensive grading of the quality of evidence and is reflected by its increasing use in international organisations such as the WHO.
49	SH	Department of Health	All	General	General	**Overview** We are content with the draft, and we are pleased	Thank you for your comment.

						with the many useful improvements to the GAD section of the Guideline. For example, the addition of clear recommendations (1.2.33 – 1.2.35) for sequenced interventions, when an initial high intensity psychological treatment or medication produces a less than adequate response, is very helpful, as is the increased clarity regarding the need for therapists to be appropriately trained and supervised.	
50	SH	Department of Health	All	General	General	**Title of the Guideline** Could you please clarify the reasons for naming the original (2004) guide the *'Anxiety Guideline'* when in fact it covers only two of the seven anxiety disorders. In our view, this decision may have contributed to the current under-treatment of the other anxiety disorders in IAPT services and in primary care. Could you please therefore consider replacing the above title with one that more accurately describes the patient population covered by the guideline (for example, GAD and panic disorder only).	Thank you for this comment, the title of this guideline has now been amended to: "*Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care (partial update).*"
51	SH	Department of Health	NICE	1.2.14	14	**Use of outcome measures** This page of the draft short guidance includes the helpful recommendation that individuals' progress during guided self-help or psycho-education groups should be monitored with standardized outcome measures. However, a similar recommendation does not appear to be made for pure self-help, which we feel is rather unfortunate. We consider that, once a clinician has diagnosed GAD and has decided to provide any intervention (including recommending pure self-help), it is desirable for the clinician to take responsibility for monitoring the effect of the intervention, and for planning a subsequent intervention if necessary. We would therefore advocate that a follow-up meeting, at which a symptom measure is re-administered, should be scheduled whenever pure self-help is recommended.	Thank you for this comment which we have considered, but decided not to include the suggested change. While in some service contexts, for example IAPT services where a self-help text is recommended by a Psychological Wellbeing Practitioner it may well be good practice for the clinician to schedule a review appointment, in other contexts as when recommended by a GP, we consider it may well be appropriate for the clinician to suggest to the patient to see how they get on and make a follow up appointment if needed.
52	SH	Department of Health	NICE	1.2.16	15	**Definition of 'marked functional impairment'** The partial update recommends that people with	Thank you for your comment. A specific definition of marked functional impairment is

						GAD should be offered high intensity psychological treatment or medication immediately, if there is 'marked functional impairment'. In our opinion, it would be helpful if a definition of "marked functional improvement" could be included in the update. Otherwise, potential confusion could well arise among clinicians as to which people should go straight to high intensity intervention.	not helpful as this may refer to different things in variable contexts (i.e. primary care or secondary care) for different individuals. This is often a matter of clinical judgement.
53	SH	Department of Health	NICE	1.2.18 & 1.2.19	15 -16	**Number of sessions of high intensity psychological therapy** The partial update helpfully reviews the data on a number of therapy sessions that were offered in trials of CBT or AR. Following on from this review, it recommends (1.2.18 and 1.2.19) that both treatments *'should typically consist of 12 – 15 weekly sessions, each lasting one hour'*. In our view, it would be more helpful if the phrasing were to read: *'..should consist of up to 12 – 15 weekly sessions, each lasting one hour'*. This is because generalisation studies have found that results as good as those achieved in trials can be obtained in routine practice with a substantially smaller median number of sessions, if therapists are allowed to go up to the number of sessions offered in the trials if necessary, but can also discharge clients beforehand if recovery occurs more quickly (please see Gillespie et al. 2002, *Behaviour Research and Therapy,40,* 345-357 for an example of such a study). We believe that Commissioners could find the suggested rephrasing more acceptable, and we are reasonably confident that it will not affect the quality of therapy that clients receive.	Thank you for your comment. As you note, the number of sessions recommended was based on the evidence reviewed. However, this recommendation is clearly not intended to require people with GAD to continue longer in treatment than they need if they have recovered sooner than 12 - 15 sessions. We considered your suggested alternative wording, but were concerned that this might be misunderstood as setting a maximum of 12 - 15 sessions and people with GAD who require longer treatment might be denied this. Instead we have altered the wording as follows: "Should typically consist of 12-15 weekly sessions (fewer if the person recovers sooner; more if clinically required), each lasting one hour".
54	SH	Department of Health	NICE	General and 1.4.6	25	**Problems generated by the decision not to update the Panic Guideline except for the cCBT** The stepped care model in the 2004 guideline involved five steps and focused as much on where treatment should be delivered (primary care, secondary care, etc) as on the particular	Thank you for your comment. The remit for this guideline was to update cCBT for panic as part of the technology appraisal update (NICE, 2006 TA97). We were not asked by NICE to update the full clinical guideline for panic disorder and are therefore unable to update the stepped care model.

						type of treatment that should be provided. As IAPT has intentionally blurred the boundaries between primary and secondary care, the five-step model appears to be out of date and confusing. This is recognised in the updated GAD section,.where a four-step model is now proposed, and which focuses more exclusively on what interventions should be delivered at each step (rather than where they might be provided), and is similar to the model in the revised depression guideline. We welcome this change. However, it makes the unchanged panic disorder stepped care model seem even more out of date. Could you please therefore consider the adoption of a four-step format for panic disorder also. The 2004 Anxiety Guidance and the 2004 Depression Guidance both recommended that if 'depression and anxiety' are present, then treatment should initially focus on depression. We believe that this recommendation was unhelpful, because the term 'anxiety' does not refer to a psychiatric disorder. Therefore, it appears to be unclear as to whom the recommendation applied. We consider that it also failed to recognise that, in many people with a pre-existing anxiety disorder, a more recent episode of depression may be largely secondary demoralization that will respond well to treatment that focuses on helping the person overcome the anxiety problem. The revised 2009 depression guidance recognises these points, and now includes a more nuanced and useful statement about co-morbidity (recommendation 1.4.1.1 of the 2009 depression guideline). In our opinion, this statement should be transferred, with suitable amendment, to the GAD and panic disorder update, replacing recommendation 1.4.6 (please see page 25 of the draft short guidance).	As stated above, it was our remit to only update recommendations specific to generalised anxiety disorder. In the GAD section of the NICE guideline we made this recommendation: 'For people with GAD and a comorbid depressive or other anxiety disorder, treat the primary disorder first (that is, the one that is more severe and in which it is more likely that treatment will improve overall functioning)' which mirrors the Depression update guideline (2009). We have removed the recommendation from the original guideline, 1.4.6.
55	SH	Department of Health	NICE	4.2	37	[Also 1.4.37 page 31 NICE version]	Thank you for your comment.

						cCBT We note that “Fearfighter” (a form of cCBT) is recommended for panic disorder. We would ask whether there is any reason why none of the "free to air" cCBT packages are also recommended. You are no doubt aware that there is a cost to “Fearfighter”. Could you please clarify this. We think that the update review of cCBT for panic disorder in the Draft full Guidance is scholarly and helpful, but the clinical recommendation (support for “Fearfighter”) does not appear to follow from the review. Could you please reconsider this. The HTA recommendation for Fearfighter is transferred into the new guideline uncritically, even though the new narrative review that is included in the full guidance suggests that Fearfighter has not been shown to be superior to any control condition on measures of panic attacks. For consistency therefore, one could argue that the recommendation for Fearfighter should be removed from the panic guideline and instead, its recommendation should be reserved for the future phobias guidance. Alternatively, if NICE feels that the recommendation should stand then, in our opinion, it should be qualified to explain that Fearfighter has only been shown to have a specific effect on the phobic avoidance associated with panic disorder. We feel therefore that its use should be restricted to individuals with panic disorder and agoraphobia. The draft full anxiety guidance reviews non-UK cCBT programmes for panic disorder and concludes that both the Swedish programme (Internet Psykiatri) and the Australian programme (Panic Online) are cost-effective. Although both programmes are supported in the extensive literature review, neither is recommended in the short guidance, because neither are available in the UK at the moment. In the case of Internet Psykiatri, the reason for the lack of availability	FEAR FIGHTER We acknowledge Department of Health’s concern regarding the recommendation for Fear Fighter. After discussion, we decided to exclude the review of “Fear Fighter” in this update for the following two reasons. Firstly, only one-third of the population were diagnosed with panic disorder, whilst the majority were diagnosed with phobia. This does not meet our inclusion criteria for a partial update of CCBT for panic disorder. Secondly, the existing health economic analysis for Fear Fighter in the NICE TA was based on phobia outcomes. Therefore the health economic analysis would not apply to a panic disorder only population. PANIC ONLINE We acknowledge the fact the successor of PanicOnline – PanicStop is available in UK as stand-alone program. After discussion, we decided only a research recommendation will be made for the following reasons. Firstly, there are no available good quality studies evaluating PanicStop. We can only estimate the effect by extrapolating from PanicOnline trials. However, PanicOnline is not directly similar to PanicStop. We contacted the developer of the program. Although the key components of both programs are the same, PanicOnline is a much briefer program with shorter modules. Panic Stop makes far more use of audio, video, online interactives, etc, than Panic Online. Secondly, PanicOnline is a therapist assisted program and PanicStop is a self-automated program without any therapist assistance. It is unclear whether therapist assistance is essential for the program to work. It is therefore concluded the effect of therapist

						would appear to be obvious; the programme is written in Swedish, and we consider that there can be very few UK panic disorder sufferers who are fluent in that language. With regard to Panic Online, the self-help fully automated treatment programs (Panic Stop! and GAD Online) are available to non-Australian residents, including UK citizens. The therapist-assisted versions only are restricted to Australian citizens. Health professionals (psychologists, GPs, psychiatrists, mental health nurses, OTs and social workers) can also register to receive full 'read only' access to the treatment programs (please see: https://www.anxietyonline.org.au/health-professionals). It therefore appears that Panic Stop! (the successor the Panic Online, which is regarded positively in the guideline and is essentially an extended version of the original programme) is available in the UK as a stand alone non-supported or fully automated cCBT programme. Furthermore, health professionals can also use the same materials to support their patients in the UK if they are using Panic Stop! As this is the case, could you please consider including Panic Stop!/Panic Online in the guideline.	assisted PanicOnline cannot be extrapolated to self-automated PanicStop. For the reasons above, the research recommendation will stand.
56	SH	Department of Health	All	General	General	**Scope of the Revision** We were concerned to find that in panic disorder, the revision only covers cCBT. Since the original guideline was published in 2004, several RCTs of medication and/or psychological therapies for panic disorder have been published, including a positive trial for a therapy (brief psychodynamic) that was not recommended in the 2004 guideline. Ideally, we would like to see the remit of the	Thank you for your comment. The remit for this guideline was to update CCBT for panic as part of the technology appraisal update (NICE, 2006 TA97). We were not asked by NICE to update the full clinical guideline for panic disorder.

						update widened, to include medication and all psychological therapies for panic disorder. If this is not possible, could you please indicate when a complete update is likely to be attempted.	
57	SH	Department of Health	All	General	General	**Possibility that some relevant studies have not been considered.** Cochrane recently published a review of short-term psychotherapies. Some colleagues have expressed the opinion that the review contains relevant studies on GAD that were not considered as part of the partial update process. We would be grateful if you could check NICE's database against the Cochrane review, and consider any studies that may have been inadvertently omitted.	Thank you for your comment. We are aware of the Cochrane Review published in 2010 and cross-checked the references. We have included all studies that matched our methodology criteria, and excluded those did not (i.e. we excluded non RCTs and studies using DSM III diagnostic criteria).
58	SH	Department of Health	All	General	General	**Scope of the cost-benefit analyses** The cost-benefit analyses included in the partial update seems to be unduly focused on symptomatic improvement. IAPT has always argued that well-delivered psychological therapies also have a broader social impact, such as changes in the receipt of benefits, in employment and ian productivity while at work. We would ideally like to see these broader social impacts included in the cost-benefit analyses. When this cannot be done (because, say the data is not available), we feel that it would be helpful if the limitations caused by the absence of data could be clearly stated.	According to the NICE methods of technology appraisal (NICE, Guide to the Methods of Technology Appraisal, June 2008): "The perspective adopted on costs should be that of the NHS and PSS. Technologies for which a substantial proportion of the costs (or cost savings) are expected to be incurred outside of the NHS and PSS, or which are associated with significant non-resource effects other than health, should be identified during the scoping stage of an appraisal. In these exceptional circumstances, information on costs to other government bodies, when these are not reflected in HRQL measures, may be reported separately from the reference-case analysis. The intention to include such data will normally be agreed with the Department of Health before finalisation of the remit". In addition, the same document states: "Productivity costs and costs borne by patients and carers that are not reimbursed by the NHS or PSS are not included in either the reference-case or non-reference-case analyses". The area of anxiety is not considered to incur substantial costs beyond NHS & PSS (compared with other areas of health).

							Therefore, the economic analyses undertaken for the partial update on anxiety adopted the standard NHS & PSS perspective recommended by NICE; changes in the receipt of benefits were beyond this perspective. Productivity losses are not included in either the reference-case or non-reference-case analysis, following NICE guidance, because such losses are also reflected in HRQL measures and their inclusion would result in double-counting. The perspective of the costs to be considered was also stated in the scope of the guideline update (under the "economic considerations" subheading): "Costs will be considered from an NHS and personal social services (PSS) perspective".
59	SH	Lundbeck	Full	8.8.2	291	'Sertraline was included in the economic analysis, despite the fact that it is not licensed for the treatment of patients with GAD, because it is routinely used for this purpose in clinical practice in the UK.' Our comments are related to the choice of this drug in the economic model because sertraline is included without any references to support its use in real practice. In addition, the evidence on sertraline in GAD may be most limited compared to other included drugs due to the smallest number of studies (2) included in the mixed treatment comparison.	Thank you for your comment. We have now amended the guideline text to clarify that sertraline is widely used in the UK for the treatment of depression and mixed depression and anxiety and that, according to the GDG, it is likely less commonly used in the treatment of GAD, but this is probably because people presenting with anxiety in primary care are not often diagnosed as having GAD. The GDG considered that the available clinical evidence (2 RCTs with 706 participants) was sufficient to demonstrate sertraline's safety and effectiveness in people with GAD. Sertraline was found to be associated with the lowest risk for discontinuation due to side effects (demonstrated in both classical and network meta-analysis) and with one of the highest response rates across drugs. The guideline economic analysis (which took into account the uncertainty underlying the clinical data) demonstrated that sertraline had 70% probability of being the most cost-effective drug at the NICE cost effectiveness threshold

							of £20,000/QALY.
60	SH	Lundbeck	Full	8.9.1	308	[Also NICE 1.2.22 & 1.2.23 – page 16] Sertraline should not be recommended outside its licensed indications, in particular as first-line option, since: 1.The benefit to risk of sertraline in this population has not been formally assessed; benefit-harm tradeoffs are more complex than what is stated in the network meta-analysis; 2. There is no maintenance data for this drug; clinically, the assessment of efficacy after 12 weeks of treatment might lead to wide differences in treatment outcomes: 3. Results of Pfizer-sponsored trials with sertraline in GAD have not been posted in ClinicalStudyResults.org, probably because sertraline is not indicated for GAD. Thus, sertraline might benefit from the publication bias compared to other drugs, included in the network meta-analysis, for which results of GAD trials are reported in registries (escitalopram, duloxetine, paroxetine, venlafaxine, pregabalin and quetiapine). 4. The recommendation to offer sertraline first, ahead of products with a marketing authorisation for GAD is contrary to the guidance on the use of licensed medicines for unlicensed applications issued by the Royal College of Psychiatrists (College report CR142;Jan 2007) as well as the General Medical Council (Good practice in prescribing medicines – guidance for doctors; Sept 2008). Both state that before prescribing off – label, medicines with a product license must have either had a proper therapeutic trial or been considered, but excluded on clinical grounds. We suggest the recommendation for drug treatment be amended in line with the guidance from these bodies as follows:	Thank you for your comments. We feel that the available clinical evidence (2 RCTs with 706 participants) is sufficient to allow the assessment of benefit-harm tradeoffs. We agree that there are no maintenance data for sertraline in GAD. Sertraline was found to be associated with the lowest risk for discontinuation due to side effects (demonstrated in both classical and network meta-analysis) and with one of the highest response rates across drugs. The guideline economic analysis (which took into account the uncertainty underlying the clinical data) demonstrated that sertraline had 70% probability of being the most cost-effective drug at the NICE cost effectiveness threshold of £20,000/QALY. We do not agree with your suggestion on changing the recommendation. We believe that available clinical and economic evidence justifies the use of sertraline in GAD, outside its licensed indication. Nevertheless, we have slightly changed the recommendation in the light of your comments ('offer sertraline' has been replaced by 'consider offering sertraline').

						‘1.2.22 If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). **Offer SSRIs with UK marketing authorisation first. However if considered unsuitable on clinical grounds, then offer sertraline because evidence from the NICE model concludes it may be** the most cost-effective drug. Monitor the person carefully for adverse reactions. [new 2011] 1.2.23 If the SSRI is ineffective, offer an alternative SSRI or a serotonin noradrenaline reuptake inhibitor (SNRI), taking into taking into account the following factors: • UK marketing authorisation for use in GAD. • tendency to produce a withdrawal syndrome (especially with paroxetine) • the side effect profile • the risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine) • the person’s prior experience of treatment with individual SSRIs (particularly effectiveness, side effects, experience of withdrawal syndrome and patient preference). [new 2011] Footnote 9: At the time of publication ([Month], [year]), sertraline did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.’	
61	SH	Lundbeck	Full	8.9.1.2 & 8.9.1.3	308	[Also NICE 1.2.22 & 1.2.23 – page 16] If NICE choose to ignore the comments outlined in point 2 above, we believe it would help clarify the recommendations for prescribers and commissioners if the guideline specifically states which antidepressants **do** hold a current UK marketing authorisation for GAD, as well as clearly indicating that sertraline **does not**. We request the recommendation wording is amended (**in all versions of the guidelines**) as follows:	Thanks for your comment. The guideline does make it clear that Sertraline does not hold a market authorisation for the treatment of GAD. We do not feel it is necessary to specify that the economic evidence came from the NICE model. We have now taken out the first bullet point in 1.2.23 referring to UK marketing authorisation as we considered it to be inconsistent with recommendation 1.2.22; therefore your suggestion is not relevant to the updated recommendation.

						‘1.2.22 If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). Offer sertraline first because **evidence from the NICE model concludes it may be** the most cost-effective drug. Monitor the person carefully for adverse reactions. [new 2011] 1.2.23 If sertraline is ineffective, offer an alternative SSRI or a serotonin noradrenaline reuptake inhibitor (SNRI), taking into taking into account the following factors: • UK marketing authorisation for use in GAD. **SSRIs with marketing authorisation are escitalopram and paroxetine. SNRIs with marketing authorisation are venlafaxine XL* and duloxetine. (*Some brand versions only – check SPC)** • tendency to produce a withdrawal syndrome (especially with paroxetine) • the side effect profile • the risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine) • the person’s prior experience of treatment with individual SSRIs (particularly effectiveness, side effects, experience of withdrawal syndrome and patient preference). [new 2011] Footnote 9: At the time of publication ([Month], [year]), sertraline did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.’	
62	SH	Lundbeck	Full	8.8.2	296	[Table 68] The unit cost of venlafaxine XL is based on Venaxx XL 75mg in BNF 59, March 2010. We would like the GDG to be aware that this branded generic does not hold a current UK marketing authorisation for GAD. In addition whilst this branded generic was the lowest cost option in March 2010, in practice prescriptions written for venlafaxine XL could be filled with branded generics which have a significantly higher unit cost. This should be taken into consideration when interpreting the relative cost effectiveness of	Thank you for your comment. The fact that a drug doesn’t hold marketing authorisation is not a strong reason for not recommending it, if the clinical and economic data are compelling for its clinical and cost effectiveness. Besides, even if this particular branded generic product does not hold a UK marketing authorisation for GAD, venlafaxine XL as a drug does.

						venlafaxine XL in the NICE model.	
63	SH	Lundbeck	Full	8.8.2	296	[Table 68] The average daily dosage for sertraline is assumed to be 100 mg, but no references (guidelines, data analyses, etc) provided support this assumption. It would help clarity if this were included.	Thank you for your comment. In the guideline we state: “The average daily dosage of each drug was determined according to optimal clinical practice (GDG expert opinion) and was consistent with the respective average daily dosage reported in the RCTs considered in the economic model”. Two RCTs on sertraline were included in the economic model: In ALLGULANDER 2004, after a tapper period, the daily dose ranged between 50-150mg, with average being just below 100mg/day. In BRAWMAN-MINTZER2006 the average daily dose was 150mg. According to the GDG expert opinion, a 100mg dose of sertraline is equivalent to 20mg of paroxetine or 10mg of escitalopram.
64	SH	Lundbeck	Full	8.8.2	299	[Table 69] The number of GP visits is estimated from an ‘expert opinion’ while in the NICE review of existing models, using such a source resulted in partial acceptance by NICE. Hence clarity is needed regarding NICE’s acceptance of this data source. Using real data whenever available (e.g., GPRD) could be of a higher value; however, that concerns the NICE’s model as well.	Thank you for your comment. Cost data utilised in the model included two different types of costs, as reported in the guideline: a. intervention costs b. other health and social care costs incurred by people with GAD The former, consisted of drug acquisition costs (estimated using the optimal daily dosage for each drug, consistent with data taken from RCTs included in the guideline meta-analysis, and BNF prices) and costs of GP visits. No data on the *optimal* number of GP visits required for pharmacological treatment of people with GAD are available, and therefore we had to use the GDG expert opinion for this model estimate. However, in order to estimate the latter, that is, other health and social care costs incurred by people with GAD (*including* GP visits) we did use real resource use data derived from the

							adult psychiatric morbidity survey in England (McManus et al., 2009), supported by the GDG expert opinion, as reported in the guideline. Please note that, according to NICE guidance for the development of clinical guidelines (NICE, The Guidelines Manual 2009), it is advised that "the health economist should look at pragmatic options for identifying inputs. Examples include using the clinical evidence for that key clinical issue (and perhaps other relevant issues) and liaising with the systematic reviewer, other GDG members and other experts".
65	SH	Lundbeck	Full	8.8.2	295	'The reduction in utility score due to intolerable side effects was assumed to equal the greatest utility reduction due to side effects reported for people with depression under antidepressant medication'. This implicit assumption was not clearly stated in the report.	Thank you for your comment. We have re-written the paragraph in order to add more details and clarify this issue.
66	SH	Lundbeck	Full	Appendix 18	General	In the NICE review of existing external models, whenever an impact of side effects on HRQoL was not considered, NICE concluded that all important and relevant health outcomes are only "*partly* included". However, in the model developed by NICE, the analysis did not consider any reduction in utility due to **tolerable** side effects and considered only the reduction in utility score due to **intolerable** side effects (full version page 295).	In the review of existing external models we did conclude that all important and relevant health outcomes were only 'partly included' when the impact of side effects on the HRQoL was not considered. Please note that in the review of the guideline analysis (also in appendix 18), which did at least consider the reduction in utility due to intolerable side effects (but not due to tolerable side effects due to lack of relevant data), we also concluded that all important and relevant health outcomes were only 'partly included'.
67	SH	Lundbeck	Full	8.8.2	296	'The costs of treating side effects were not considered in the economic analysis conducted by NICE'. However, when NICE evaluates already existing external models in GAD, NICE highlights that these costs are relevant. Our recommendation is therefore to consider these costs within the NICE economic evaluation. This is a confusing and conflicting stance.	We are not sure where you are referring to when you say that 'when NICE evaluates already existing external models in GAD, NICE highlights that these costs are relevant'. The review of existing economic studies in chapter 8 of the guideline does not highlight the relevance of such costs or the implications from omitting them, although, it is true, the

							potential impact of omission of such costs in the results of existing and new economic analyses should be considered and discussed. We have now discussed in more detail why such costs were not considered in the guideline economic analysis, as well as the potential impact of such an omission on the results of the analysis.
68	SH	Lundbeck	Full	Appendix 18		When costs of treating side effects are not considered, NICE concludes that not all important and relevant costs are included.	Thank you for spotting this error. None of the existing studies had considered the costs of treating side effects, and we had stated in error that all important and relevant costs were included. We have added in the assessment of all studies in appendix 18, including the guideline analysis, that important and relevant costs were partly included because costs of treating side effects were not considered (but these costs were probably not substantial). We have also discussed this issue in chapter 8 of the full guideline.
69	SH	Lundbeck	Full	Appendix 18		[Jorgensen et al. (2006)] NICE states that there are “potentially serious limitations” in the study by Jorgensen mainly due to the fact that this study was funded by H. Lundbeck (even though this study was considered directly applicable in the UK setting, and few study limitations were identified). On the other hand, most of the trials included in NICE’s MTC were industry-sponsored; therefore clarity is needed on acceptability of this weakness by NICE for future studies/submissions.	Potential conflicts of interest (e.g. a conflict of interest relating to industry-funded studies) is one of the criteria for the assessment of the methodological quality of economic studies, according to the NICE methodology checklist for economic evaluations (please see NICE, *The Guidelines Manual 2009*, Appendix H). On the other hand, the guideline economic analysis is not related to such conflicts of interest. It is true that most trials included in the network meta-analysis that informed the guideline economic model were industry-funded. Potential conflicts of interest have been taken into account at the assessment of both clinical and economic evidence considered in the guideline. Jorgensen *et al.* (2006) was judged to have ‘potentially serious limitations’ because it was industry funded, the impact of side effects on HRQoL was not considered at all, and limited

							sensitivity analysis was conducted. In contrast, the guideline economic analysis was judged to have 'minor limitations' because there were no potential conflicts of interest, the impact of intolerable side effects on HRQoL was considered (although the impact of tolerable side effects was not and this was acknowledged as a limitation of the analysis), and probabilistic sensitivity analysis was conducted. Please note that the Jorgensen study was considered 'directly applicable' even though it did not measure outcomes in terms of QALYs, which is the outcome preferred by NICE, because escitalopram was found to be dominant; therefore interpretation of the results was easy, despite non-use of QALYs. In any case, the guideline meta-analysis, which utilised response data from 25 RCTs synthesised using network meta-analysis, demonstrated that sertraline was more cost-effective than paroxetine at the NICE cost-effectiveness threshold of £20,000/QALY, which is consistent with the findings of the Jorgensen study.
70	SH	Lundbeck	Full	8.8.2	291	'People initiated on the first line drug could either discontinue due to intolerable side effects or continue the drug treatment for 8 weeks'. Therefore, it is considered that side effects can not occur earlier in this decision-tree.	The 8-week probability of discontinuation due to intolerable side effects gives the proportion of people that have stopped the drug by the end of 8 weeks – but discontinuation can occur at ANY point within this period. This means that in this decision tree intolerable side effects can actually occur earlier than 8 weeks. According to the GDG expert opinion, most of these discontinuations occur within the first 2 weeks following initiation of treatment, so for purposes of model structure only we assumed that, for people discontinuing, switching to the next drug would occur at the end of 2 weeks from drug initiation. We have clarified this point

							in the final draft. However, probability of people discontinuing due to side effects, as estimated in Network Meta-analysis and utilised in the model, takes into account the total number of people discontinuing from time zero from initiation of treatment, and up to t=8 weeks.
71	SH	Lundbeck	Full	8.8.2	292	Relapse can occur after response and not after remission (not considered in this decision-tree), that is not in accordance with the standard definition of relapse.	The model structure did not include a state of 'remission', but rather a state of 'no relapse' at the end of the 6-month maintenance treatment following response. The model states are described in the model structure – we apologise for the error in the schematic diagram, where following 'no relapse' there is 'remission' in parenthesis. We have now corrected the diagram (by deleting 'remission'). The model structure/health states were dictated by the availability of appropriate clinical and utility data considered in the guideline systematic review. The guideline systematic review included data on both response and remission. Utilisation of both types of data was not possible, because not all studies provided data on both outcomes so as to estimate the numbers of people with GAD who responded to treatment but did not meet criteria for remission, and of those who responded to treatment and remitted. For the economic model, it was decided to utilise response (rather remission) data for the following reasons: 1. Response data were available from a larger number of studies , including a higher number of participants; 2. Clinical data on relapse, which were utilised in the model in the form of a 6-month probability of relapse, referred to people who had *responded* to treatment and not to people

							who had *remitted*. No relapse data following remission were available in the literature. 3. Utility data were available for the health state of 'response' but not for the health state of 'remission'; in addition, the utility data used in the model, taken from one of the studies that also provided data on relapse (Allgulander et al, 2006), referred to the health states of 'relapse following response' and 'no relapse following response' – which were the health states we modelled. No utility values on 'relapse following remission' where identified in the literature. We have added a paragraph in the final guideline text discussing this issue. It is true that some people who have responded and have subsequently not relapsed in the model may have actually remitted, and they may relapse at a later stage. However, the model did not consider these further stages of the course of GAD, due to lack of appropriate clinical and utility data. The state of 'no relapse following response' is an endpoint of the model. In any case, the rates of relapse following remission are low and definitely much lower than the relapse rates following response (see Yonkers et al, Phenomenology and course of generalised anxiety disorder. Br J Psychiatry 1996; 168: 308-13), which means that non-incorporation of such an event is likely to have had a small impact on the model outcomes.
72	SH	Lundbeck	Full	8.8.2	292 & 298	In table 69 (page 298), only one probability of relapse under active treatment is documented while in figure 6 (page 292) that describes the model structure, relapse can occur on different time horizons (26 weeks or 26+8=34 weeks)	In all arms of the model, the probability of relapse refers to the time period of 26 weeks ***from the point of response to treatment***, expressing the proportion of people that relapsed during the 6 months of maintenance

						depending on whether patient experienced a switch or not. This may imply an underestimation of relapse rates when patients experienced no treatment switch, and is not discussed in the report.	treatment. The endpoint of this period (maintenance treatment) is at 8+26 = 34 weeks for people who did not switch drug due to lack of response, or 8+8+26=42 weeks for people who switched drug due to lack of response and had a second 8-week treatment that led to response. The exact end point of this period (e.g. at 34 or 42 weeks) is not relevant as long as the model has considered and applied a 6-month probability in all arms.
73	SH	Lundbeck	Full	8.8.2	293	'The probability of conditional response for the second-line drug in each arm of the model was calculated as the average probability of conditional response of all drugs except the one that was used as first-line treatment in this particular arm of the model'. However, response rate for a drug is probably lower in second-line than in first-line. Implications of this implicit assumption are not discussed	Thank you for your comment. We have now discussed this issue and its implications in the final guideline text. We have also conducted a sensitivity analysis in which we reduced the response of the 2nd line drug by 15%, and we found that results remained unaffected under this scenario. We have included this extra analysis in the final guideline.
74	SH	Lundbeck	Full	8.8.2	293	The probability of response is defined in case of no discontinuation due to side effects. However, to calculate these probabilities, individual patient data are required (in order to include patient with discontinuation due to lack of efficacy but exclude patients who discontinued due to tolerability) and these data are not available in all studies included in the network meta-analysis.	The rate of conditional response was estimated as the **number of people in each arm of a trial responding to treatment** divided by the number of **all participants in the arm** excluding **those who discontinued due to side effects**. People who discontinued treatment for any reason were considered as non-responders in the guideline meta-analysis, according to ITT (intension-to-treat) approach. All 25 studies included in the network meta-analysis of conditional response provided data on the 3 outcomes highlighted in bold, above. Therefore, it was possible to estimate rates of conditional response from each trial arm included in the network meta-analysis. We have clarified this point in Appendix 14.
75	SH	Lundbeck	Full	General	General	The recommendation of sertraline as first line treatment within GAD for which it does not have a regulatory approved indication is intriguing. It can be foreseen that it will have several consequences for future drug development, and	Thank you for your comments. The trials included in the network meta-analysis, confirmed by traditional meta-analysis, show that sertraline is the most cost-effective drug for GAD by a very great margin. The trials for

						for general clinical practice in the UK. Firstly, the recommendation of sertraline, without the approved indication questions the importance of proper diagnosis. What would be the incentives for a proper indication, if sertraline is the preferred drug therapy anyway; this is detrimental to primary care psychiatry. Drug development would suffer from this, and the incentive for developing (and researching, and understanding) in a number of indications will be lost. Also, by the guideline, sertraline would not qualify as a 2nd line treatment as it does not have an MAA in the indication. The lack of documentation of efficacy, including long-term is critical. Unless NICE and the regulators from now on would be happy transferring long-term efficacy data from one indication to another.	sertraline included were, admittedly, few in number (N=2), although the number of participants were nearly 750. Moreover, the clinical effect was significant and, again, not small. Added to this the substantially lower acquisition cost resulted in this drug being clearly dominant in the economic analysis. We do agree with you that it would be better to have longer term data. This is a common experience in guideline development: drug companies very rarely produce long term data. On balance, the GDG still wish to recommend sertraline on the basis of the evidence we have seen. However, we have changed the recommendation to "consider offering sertraline" rather than "offer sertraline" in light of the fact that we have only two trials and no longer term data. The GDG discussed you comments and do not agree that recommending sertraline on this basis will create the problems you suggest for drug development, primary care psychiatry or proper diagnosis (although the GDG didn't quite understand this latter point).
76	SH	Lundbeck	Full	General	General	For some of the non-pharmacological interventions, the efforts seem to be quite costly, and we question how well it has been factored in all the HTA evaluations, and if all the demographic, and geographic limitations of these treatments have been appropriately considered.	Direct comparison between psychological and pharmacological interventions regarding their cost effectiveness was not possible, for the reasons explained in 6.6.2 (6.6.3 of the final draft) and 7.6.2 (7.6.3 of the final draft). We have now added these reasons in the economic section of chapter 8. The GDG considered all the available evidence on the relative benefits, harms and costs of psychological and pharmacological interventions, as well as implementation issues (including potential demographic and geographic limitations) before making recommendations.

77	SH	Lundbeck	Full	8.9.2	310	In terms of the research proposals, the proposals by NICE are not clinical studies that pharmaceutical companies could easily conduct particularly because regulatory bodies would probably not look favourably to large studies being conducted using drugs not approved for the indication.	Thank you. This is understood. The notion was that these clinically informative and pragmatic trials would be supported by the NHS rather than pharmaceutical industry.
78	SH	National Treatment Agency for Substance Misuse	NICE	General	General	The NTA welcomes the partial update and the reference to substance use as a common occurring co-morbid disorder.	Thank you for your comment
79	SH	National Treatment Agency for Substance Misuse	NICE	1.2	10 -21	Although there is a statement at 1.2.8 about the treatment of those with alcohol problems and generalised anxiety disorder, there is no similar statement with regards to drug problems. The NTA would welcome a statement on treating drug misuse for people with GAD and drug misuse problems.	We have changed the relevant recommendation to include all substance misuse (drugs as well as alcohol).
80	SH	National Treatment Agency for Substance Misuse	NICE	1.2.36	19	This suggests that a referral to step 4 should be considered for “significant co morbidities, such as drug misuse”. There may be benefit to referral to drug treatment prior to this point and this may be covered in addressing the earlier point (example 3).	Thank you for your comment. As mentioned in our response to comment 103, we have changed the relevant recommendation to include all substance misuse.
81	SH	National Treatment Agency for Substance Misuse	NICE	6	41 -42	The section on ‘Related NICE guidance’ should perhaps include references to NICE drug misuse clinical guidelines 51 and 52, which make explicit reference to the anxiety guideline.	Thank your for your comment; we have added the clinical guidelines on drug misuse.
82	SH	NETSCC-HTA Ref 1	Full	General	General	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** I am not aware of any	Thank you for your comment.
83	SH	NETSCC-HTA Ref 1	Full	3.5	32	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE’s Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guideline**	Thank you for your comment.

						smanual). The systematic review of the clinical literature appears to have been very comprehensive and well conducted	
84	SH	NETSCC-HTA Ref 1	Full	3.6	45	Again the systematic review appears to have been comprehensive	Thank you for your comment.
85	SH	NETSCC-HTA Ref 1	Full	General	General	Overall the search and analytical methods used for the systematic review are appropriate	Thank you for your comment.
86	SH	NETSCC-HTA Ref 1	Full	6.2	111	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** The statistical methods used to analyse the data are appropriate and the conclusions drawn are correct	The whole chapter refers to mixed anxiety population (please see 6.3.1), therefore it is unnecessary to insert a subheading for each paragraph.
87	SH	NETSCC-HTA Ref 1	Full	6.3	116	The statistical aspects of this section and the conclusions drawn are appropriate	Thank you for your comment
88	SH	NETSCC-HTA Ref 1	Full	6.4	124	The analysis of the data and the conclusions drawn are limited by their being only 2 studies in this section	Thanks for your comment. The assessment of quality of the evidence has taken that into account already. For clarity purpose, a note will be added in the chapter about this limitation.
89	SH	NETSCC-HTA Ref 1	Full	7.3	155	The statistical methods used to analyse the data are appropriate and the conclusions drawn are well explained	Thank you for your comment
90	SH	NETSCC-HTA Ref 1	Full	7.6	178	Statistical methodologies and conclusion appropriate	Thank you for your comment
91	SH	NETSCC-HTA Ref 1	Full	8.2	201	The statistical aspects of this section are correct and the conclusions are well explained	Thank you for your comment
92	SH	NETSCC-HTA Ref 1	Full	8.3	231	The statistical aspects of this section are correct and the conclusions are well explained	Thank you for your comment
93	SH	NETSCC-HTA Ref 1	Full	8.4	248	Statistical methodologies and conclusion appropriate	Thank you for your comment
94	SH	NETSCC-HTA Ref 1	Full	General	General	There are a number of borderline results where point estimate suggests a positive result but confidence interval contains one or zero suggesting not statistically significant results. Authors could possibly provide an explanation of relevance of these results in the introduction	Thank you for your comment. This issue of borderline results have been dealt with in GRADE profiles, where studies with borderline results are downgraded for quality.
95	SH	NETSCC-HTA Ref 1	Full	General	General	There appears to be a number of appendices missing 16b, 17c, 19c etc. which are referred to	These appendices were not missing and are available on the NICE website.

						through-out the text for forest plots and other statistical tables	
96	SH	NETSCC-HTA Ref 1	Full	General	General	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** The recommendations have been drawn from the evidence available and the findings of the analysis.	Thank you for your comment.
97	SH	NETSCC-HTA Ref 1	Full	General	General	The recommendations are reflective of the evidence and are not over-stated.	Thank you for your comment.
98	SH	NETSCC-HTA Ref 1	Full	General	General	As far as I'm aware all aspects of the evidence have been included in the study	Thank you for your comment.
99	SH	NETSCC-HTA Ref 1	Full	General	General	**3.2 Are any important limitations of the evidence clearly described and discussed?** The authors have provides a very comprehensive discussion of their results and findings	Thank you for your comment.
100	SH	NETSCC-HTA Ref 1	Full	General	General	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** As a non-clinical person I found the report very readable and easy to understand	Thank you for your comment.
101	SH	NETSCC-HTA Ref 1	Full	General	General	There is a good explanation of how the recommendations have been linked and there is a clear pathway from the evidence presented to the recommendations made	Thank you for your comment.
102	SH	NETSCC-HTA Ref 1	Full	General	General	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** The research recommendations are justified	Thank you for your comment.
103	SH	NETSCC-HTA Ref 1	Full	General	General	My only criticism of the report is that a number of the appendices appear to be missing	These appendices were not missing and are available on the NICE website.
104	SH	NETSCC-HTA Ref 2	Full	General	General	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** Declared intentions fulfilled	Thank you for your comment.
105	SH	NETSCC-HTA	Full	Gener	General	**2.1 Please comment on the validity of the work**	Thank you for your comment.

		Ref 2		al		**i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).** Quality of methods generally very good. See below for specific issues relating to the economic analyses.	
106	SH	NETSCC-HTA Ref 2	Full	5.4.6.1	104	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** In relation to the statement, "Cost-benefit analyses should also be carried out", do the authors mean cost-benefit analysis specifically or do they mean economic evaluation more generally, i.e. including cost-effectiveness/cost-utility. The use of the term CBA seems rather strange in this context, given the preference from NICE for CEA/CUA.	Thank you for spotting this error. We meant economic evaluations in general. We have amended the text in the light of your comment.
107	SH	NETSCC-HTA Ref 2	Full	6.6.2	132	Given that the methods in chapter 3 state that "economic studies were included if they used clinical effectiveness data from an RCT, a cohort study, or a systematic review and meta-analysis of clinical studies", it is unclear why this section states, "no RCTs…were identified". The authors should clarify whether their review focuses on RCTs alone or a wider range of study designs. Alternatively, if different designs were included for different purposes, this should be made clear in the methods.	Thank you for the comment. There is a difference in inclusion criteria between the clinical and economic literature review. The inclusion criteria you are quoting from chapter 3 refer to studies considered in the Economic literature review. In chapter 6, section 6.6.1 of the first draft (now 6.6.2) refers to the economic literature review on low intensity psychological interventions. In this section we state that the systematic review of economic literature did not identify an economic studies meeting the inclusion criteria listed in chapter 3. Section 6.6.2 of the first draft (now 6.6.3) is not relating to the search/review of existing economic literature, but to the guideline economic analysis on psychological interventions. In this section we report that "no RCTs comparing directly low-intensity

							psychological interventions with other active treatments (high-intensity psychological interventions or pharmacological treatments) that could provide clinical input parameters for a modelling study were identified in the systematic clinical literature review". The guideline systematic review of clinical literature on this area (low intensity psychological interventions) included only RCTs and quasi-RCTs, as reported in section 6.1.3 and table 6 of the full guideline.
108	SH	NETSCC-HTA Ref 2	Full	6.6.2	132	Similarly, it's not clear why the search was limited to interventions compared to other active treatments. This is not noted as an inclusion criterion in the methods and it is not consistent with the comparisons presented in the clinical effectiveness sections. Again, this probably just needs clarification and what would help this enormously is if the economic sections have a clearly stated research question, as is provided in the clinical sections.	As we explained in a previous comment, this section does not refer to the results of the economic search (the results of the economic search in this area, i.e. on low intensity psychological interventions, are described in section 6.6.1 of the first draft, section 6.6.2 of the final draft). In any case, the search for economic evidence was not limited to interventions compared with other active treatments. Section 6.6.2 of the first draft (6.6.3 of the final draft) refers to the attempt to develop an economic model comparing low intensity psychological interventions with high intensity psychological interventions and/or pharmacological interventions, which are all 'active' treatments. In addition, we attempted to make comparisons between different low-intensity psychological treatments. These economic questions were prioritised by the GDG, and this has now been clarified in the final guideline. In order to make this comparison we looked at all clinical evidence included in the guideline systematic review, looking for data that would allow either direct (head-to-head) or indirect (against a common baseline, which can be an

							'inactive' treatment) comparisons between low intensity psychological interventions and high intensity psychological / pharmacological interventions. We reported that the guideline clinical literature review did not identify any direct comparisons. We then looked for studies that would allow indirect comparisons. We reported in this section that indirect comparisons were problematic due to a number of (listed) reasons. If you look at the first bullet point referring to the comparators, it says "studies on psychological interventions used mainly a **waiting list** or **standard care** as a comparator, while studies on pharmacological treatments used **placebo** as control". Thus, it is clear that we did consider clinical studies that included inactive treatments, in order to attempt to compare low intensity psychological interventions with other active treatments. We have added the economic research questions as well as GDG priorities for economic modelling in all economic sections in the full guideline. The priorities for economic modelling are also provided in the economic plan in appendix 15.
109	SH	NETSCC-HTA Ref 2	Full	6.6.2	133	I'm a bit confused about why an exception was made for computerised CBT using data from a study with a wait list control. If it's ok to use data on one low intensity intervention vs. WLC, why was it not ok to model data on the other low intensity interventions vs. WLC or a similar non-active comparator? Again, there is a need for a clear economic research question.	We have clarified this point in the final draft. As we also explain in a previous comment, we attempted to develop a model comparing low-intensity psychological interventions with other active treatments because this was deemed a priority by the GDG. For this purpose we looked at all clinical data included in the guideline systematic review, considering potentially relevant data on both active and inactive treatments. In the case of CCBT we made the decision to compare it against an inactive treatment (although such a comparison was not a priority

							for other low-intensity psychological interventions) because, as reported in the guideline text, the guideline is also updating the NICE TA97 on computerised CBT for anxiety (which already included economic modelling on cCBT for anxiety), and the only clinical data available for cCBT were against an inactive treatment (waiting list). All the above issues have been clarified in the final guideline.
110	SH	NETSCC-HTA Ref 2	Full	6.6.2	134	In relation to the costing of psychoeducational groups, the authors estimate the number of participants to be between 10 and 30. What is this range based on as 30 seems pretty high for a group intervention?	Please look at section “6.5. Modes of delivery”, in subheading “psychoeducational groups”. It is reported that in the clinical studies included in the guideline systematic review “the average size of groups was 20-24 participants with a total of two therapists per group”. The GDG decided to estimate the intervention cost for a wide range of participants. Considering the available clinical data, 30 is not an unrealistic highest estimate of the range.
111	SH	NETSCC-HTA Ref 2	Full	6.6.3	139	In relation to the utility data taken from Allgulander and colleagues (2006), the authors note that the definition of response in Allgulander and colleagues is different from that in TITOV2009. Can the authors explain how they differ and whether some adjustment was made to take this difference into consideration? Also, does the difference in definition explain why the relapse scores are so high (i.e. in comparison to the response scores)?	Please refer to the ‘clinical input parameters of the economic model’ in this section, where we provide the definition of response in TITOV2009. Please, also refer to the ‘utility data and estimation of QALYs’ for a definition of response, as well as a definition of relapse, in the study by Allgulander and colleagues. The definition of response in the two studies was made using two different clinical scales, and therefore no adjustment was able to be made. We are not sure what you mean in the second part of your comment: the difference in definition applies only to the definition of response. Relapse was not defined in TITOV2009, because the study did not measure relapse. The economic analysis on cCBT modelled relapse using clinical data from another guideline meta-analysis, as described

							in 'clinical input parameters of the economic model'. The definition of relapse in studies included in the meta-analysis varied, but was considered clinically similar (hence, data were pooled together in the guideline meta-analysis). Please note that one of the studies included in the guideline meta-analysis of relapse prevention was that of Allgulander et al, which provided the utility data (including relapse) for all guideline economic models. Given the definition of response and relapse in Allgulander et al, we don't consider the relapse scores to be particularly high.
112	SH	NETSCC-HTA Ref 2	Full	6.6.3	140	"The worry programme is available for research purposes only; therefore no license fee was considered at the estimation of the intervention cost, although this cost component, which may be considerable, needs to be taken into account in the assessment of cost effectiveness of other CCBT packages available in the future for the management of people with GAD." This strikes me as an area of uncertainty that might be worth assessing in sensitivity analysis?	We agree that this is an area of uncertainty. Nevertheless, if such a package is developed within the NHS, then the license fee is going to be zero (as in the guideline economic model). If, on the other hand, a commercial cCBT package is developed, we do highlight the need to consider license fees at its evaluation, along with its effectiveness and related resource use. However, the purpose of this modelling exercise is not to indicate to potential manufacturers the range of the license fee that would make a commercial cCBT product cost-effective within the NHS.
113	SH	NETSCC-HTA Ref 2	Full	6.6.3	140	Assuming the Titov study was carried out in Australia/NZ, have the authors made any judgement about how relevant the services are for a UK population? Did they consider using costs of cCBT as estimated in UK studies in sensitivity analysis?	The cCBT package described in the Titov study is considered to be relevant to the UK population, and it can be provided by health professionals working for the NHS. The costs associated with the use of the package were modelled by combining resource use reported in the Titov study (which was judged by the GDG to be relevant to the UK population) with UK unit costs of health professionals with appropriate skills. Therefore, there was no need to use costs of cCBT as estimated in UK studies (in fact, taking resource use data from a UK study but effectiveness data from the Titov study would likely introduce bias). In addition, there are no UK studies estimating

							the effectiveness or costs of cCBT for people with GAD that we could derive data from.
114	SH	NETSCC-HTA Ref 2	Full	6.6.3	140	"However, it is acknowledged that CCBT could be provided by other healthcare professionals with appropriate qualifications/training." Again, sensitivity analysis would be useful here.	Thanks for your comment. This sentence aims to clarify that CCBT is not necessarily delivered by a certain type of health professional. We have added in the final text that "The unit cost of other types of health professionals that have the qualifications and skills to provide CCBT is expected to be similar [to that of clinical psychologists]". Therefore, no extra sensitivity analysis is needed regarding this aspect.
115	SH	NETSCC-HTA Ref 2	Full	6.6.3	140	"People responding to treatment and remaining improved over the 6 months post-treatment were assumed to incur zero health and social care costs, apart from the intervention cost." Would it not be more likely that there will be some GP contacts and possibly medication?	According to the GDG expert opinion, people with GAD offered cCBT, responding to it and remaining improved, do not require further GP contacts and/or medication any more than the general population. Therefore, no extra healthcare resource use was assumed for this arm of the model. We have clarified in the final text that this was an estimate based on the GDG expert opinion, and not just an assumption.
116	SH	NETSCC-HTA Ref 2	Full	6.6.3	145	Given comments above highlighting a number of areas of uncertainty that may be worthy of further exploration, I'm surprised only one one-way sensitivity analysis was carried out.	As we have explained in our responses to previous comments, we do not think that extra sensitivity analyses are needed in the suggested areas. Nevertheless, in addition to the one one-way sensitivity analysis, we have undertaken a probabilistic sensitivity analysis, in which all model input parameters have been assigned a probabilistic distribution rather than being expressed as point estimates. This analysis has resulted in the estimation of the probability of cCBT being cost-effective relative to waiting list, after taking into account the uncertainty characterising the model input parameters.
117	SH	NETSCC-HTA Ref 2	Full	7.6	195	Again, it would be helpful to have a clear economic research question.	Thank you for your suggestion. We have added the economic research questions as well as the GDG priorities for economic modelling in all economic sections in the full guideline. The priorities for economic

							modelling are also provided in the economic plan in appendix 15.
118	SH	NETSCC-HTA Ref 2	Full	7.6.2	196	As noted for section 6, it's not clear in the methods that only evaluations with active comparison groups would be considered for the economic evaluation or indeed why. Also, in this section there are plenty of head to head clinical studies from which outcome data can be taken and it may be feasible to collect service use data from elsewhere, i.e. from non-RCTs. By limiting the search to head to head RCT based economic evaluation, the authors seem to be limiting the likelihood of being able to do any modelling.	The search for economic evidence looked at all studies assessing the cost effectiveness of high intensity psychological interventions, including comparisons with both active and inactive treatments. However, the guideline economic analysis considered the cost effectiveness of high intensity psychological interventions compared with other active treatments (low-intensity psychological interventions and pharmacological interventions), as the GDG considered this issue as a priority. The guideline economic analysis attempted to utilise any clinical data included in the guideline systematic review of clinical literature, considering data from comparisons with both active and inactive treatments, as we have explained in our response to a similar comment. This issue has been further clarified in the final draft of the full guideline.
119	SH	NETSCC-HTA Ref 2	Full	7.6.2	197	"Moreover, if high interventions are delivered in groups, then the intervention cost per person is greatly reduced, as the total cost is spread…" This is clearly true but from a cost-effectiveness point of view, this has to be balanced against the possibility of reduced effectiveness of groups compared to individual intervention.	Thank you for your comment. We have added the following text at the end of this section: "It should be noted that the guideline systematic review of clinical evidence indicated that group CBT is likely effective against waitlist control on anxiety, depression and worry outcomes; however, the evidence base for group CBT is limited. In addition, no head-to-head trials have assessed the effectiveness of group CBT relative to individual CBT".
120	SH	NETSCC-HTA Ref 2	Full	8.8.2	294	"Details on the studies, their methods and reported utility data are provided in the respective section of the economic model described in 8.7.3." Should this be 6.6.3?	Thank you – it has been corrected.
121	SH	NETSCC-HTA Ref 2	Full	8.8.2	295	"Intervention costs of no pharmacological treatment related to GP visit costs only." This is a rather conservative assumption. You could in fact hypothesise that patients not receiving pharmacological intervention may use other	No pharmacological treatment referred to placebo arms of pharmacological trials. In all these trials, participants in the placebo arms received exactly the same treatment with participants in the active drug arms, with the

						services more. Sensitivity analysis?	exception of the active drug. Therefore, 'pharmacological treatment' represents exactly the same treatment (and incurs the same ***intervention*** cost) as all the other arms of the model, excluding the administration (and acquisition cost) of drug. Actually the model makes a rather conservative assumption, favouring 'no pharmacological treatment'. Given that pharmacological treatment was found to be dominated by all other treatment options and to have negligible probability of being cost-effective (due to its lower response rates), the consideration of utilisation of other services (and the addition of the respective costs) would only demonstrate more emphatically the lack of cost effectiveness of this treatment option.
122	SH	NETSCC-HTA Ref 2	Full	9.2.2.2	366	"Panic Online is a CCBT package designed for research purposes only and is not available in clinical practice. On the other hand, Internet Psychiatri is freely available on the internet for the treatment of people with panic disorder, but in Swedish. Therefore, the models did not consider a license fee at the estimation of the CCBT intervention cost. However, alternative CCBT packages designed for the treatment of people with panic disorder in the future may not be freely available. A license fee would need to be added to the intervention cost in such cases, which, if significant, may affect the cost effectiveness of CCBT." As earlier comments, this may be worth exploring in sensitivity analysis.	As we have explained in our response to a related comment, we agree that this is an area of uncertainty. Nevertheless, if such a package is developed within the NHS, then the license fee is going to be zero (as in the guideline economic models). If, on the other hand, a commercial cCBT package is developed, we do highlight the need to consider license fees at its evaluation, along with its effectiveness and related resource use. However, the purpose of these modelling exercises is not to indicate to potential manufacturers the range of the license fee that would make a commercial cCBT product cost-effective within the NHS.
123	SH	NETSCC-HTA Ref 2	Full	General	General	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** The recommendations seem well justified and complete.	Thank you for your comment.
124	SH	NETSCC-HTA Ref 2	Full	general	general	**3.2 Are any important limitations of the evidence clearly described and discussed?**	Thank you for your comment.

						Yes	
125	SH	NETSCC-HTA Ref 2	Full	general	general	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** The report is well written, readable and well presented. It is clear how the recommendations were reached from the evidence.	Thank you for your comment.
126	SH	NETSCC-HTA Ref 2	Full	general	general	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** On the whole, the research recommendations are clear and well justified.	Thank you for your comment.
127	SH	NETSCC-HTA Ref 2	Full	8.10.10.1	326	Given the comments about poor quality studies and the limited evidence in favour of a number of different herbal interventions, it's not clear why chamomile has been chosen for a research recommendation over and above any other herbal intervention. In addition, I'm not convinced there is enough good quality evidence to make any recommendation in this category.	Thank you for your comment. Please see comment 312 which explains why chamomile has been chosen for a research recommendation and the changes made with regard to gingko biloba. The GDG agree that there is not enough good quality evidence to make a recommendation and this is why we have chosen to make a research recommendation. Hopefully, this will result in higher quality and larger trials in this area.
128	SH	NHS Direct	All	General	General	NHS Direct welcome the guideline and have no comment on the content.	Thank you for your comment.
129	SH	Nottinghamshire Healthcare NHS Trust	NICE	1.2.17	14	Heavy focus on CBT. Lots of research done for CBT but there are many other psychological interventions that may suit some people better eg counselling, family interventions. Not all service users especially older people like the style and demanding nature of 1:1 CBT. Perhaps there should be more flexibility in this point for accessing other interventions where appropriate	Thank you for drawing attention to this. We have looked into other psychology interventions, however there was either no evidence of their effectiveness or the study design of these interventions did not meet our methodology criteria.
130	SH	Pfizer Ltd.	NICE	1.2	11	[Figure 1] The Stepped Care Model is clear, but for more detail and clarification on drug treatment sequencing within steps 3 & 4, we recommend a further flow diagram specifically giving details for pharmacological treatment as described in	Thank you for your suggestion. However, the GDG decided not to include more details in the flow diagram. These details are provided in related recommendations.

						sections 1.2.22 – 1.2.32 and sections 1.2.40 – 1.2.42.	
131	SH	Pfizer Ltd.	NICE	1.2.24	17	[Also FULL version 8.7: 279-287] *We welcome the recommendation: "If the person cannot tolerate SSRIs offer pregabalin rather than an SNRI". It should be noted that pregabalin has a different mechanism of action and adverse event profile compared to the SSRI and SNRI drug classes, so switching to pregabalin following SSRI intolerance may be preferable to switching to a SNRI.* Pregabalin has a novel mechanism of action for the treatment of GAD (inhibiting excitatory neurotransmission) , which differs from the mechanism of action of the SSRIs and SNRIs (modulation of monoamine-mediated neurotransmission) (Montgomery 2006). Pregabalin also has a distinctive safety and tolerability profile (Montgomery 2006). The main side effects associated with pregabalin treatment include dizziness, sedation, dry mouth, amblyopia, impaired coordination, and impaired psychomotor and cognitive function (Bandelow 2008, WFSBP guidelines) whereas the two major classes of adverse events associated with both SSRIs and SNRIs are sexual dysfunction and gastrointestinal side effects (Montgomery 2006). In patients who are suffering from insomnia/sleep disturbance, pregabalin may be appropriate due to its demonstrated effects on GAD-related sleep disturbance/insomnia (Kasper 2009, Montgomery 2006). The differences in side effect profiles between the SSRIs/SNRIs and pregabalin are apparent in section 8.7 of the full guideline and are mentioned in the BAP (Baldwin 2005) and WFSBP guidelines (Bandelow 2008). Section 8.7 of the full guideline also refers to a pooled analysis of withdrawal rates for pregabalin in the GAD RCTs across the dose range (150–	Thank you for your comment. We have amended the recommendation referring to pregabalin. Pregabalin is recommended as an option when SSRIs or SNRIs are not tolerated. However, we do not agree with your suggestion for additional recommendations on pregabalin, given that the guideline economic analysis demonstrated that this is the least cost-effective option among drugs.

						600 mg/day, n=1149) compared to the active treatment arms in these trials (alprazolam 1.5 mg/day, n=93; venlafaxine 75mg/day, n=113; lorazepam 6mg/day, n=206) and placebo (n=484). Pregabalin was found to have similar drop-out rates to placebo (11% versus 9%), whereas higher withdrawal rates were observed with venlafaxine 75 mg/day (20%), alprazolam 1.5 mg/day (13%) and lorazepam 6 mg/day (35%) (Kavoussi 2006). We also suggest that pregabalin is additionally recommended as a treatment option later on in the treatment *pathway to allow for clinical flexibility in treatment sequencing*. We recommend adding the following to 1.2.24: "If a patient is treated with a SNRI (as per 1.2.23), and this drug is not tolerated, offer pregabalin." We recommend adding a new bullet point after 1.2.24: "In the event of neither SSRI/SNRI providing adequate effectiveness, offer pregabalin". Please see comment 4 below for details of the RCT assessing pregabalin in refractory patients (Miceli 2009).	
132	SH	Pfizer Ltd.	NICE	1.2.29	18	[Also FULL version 2.24: 16] Research indicates that GAD is the most prevalent anxiety disorder in the elderly (Flint 1994, Beekman 1998) with an estimated prevalence of 2.9% (Schoevers 2003). Therefore, special considerations for the elderly population should be included in this guideline. We recommend similar considerations for patients over 65 years old as those in the BAP guideline: "Treat as for patients younger than 65 years being mindful of the possibility of drug interactions, physical comorbidity, the need for lower doses due to reduced metabolism, or increased	Montgomery 2008 was specifically mentioned in the chapter. However, it was the view of the guideline development group that there was insufficient data to make strong recommendations concerning the efficacy of specific drugs for patients over 65.

						sensitivity to adverse effects." (Baldwin 2005). *We ask that the guideline specifically refers to randomised controlled trials carried out in this elderly population (e.g. Montgomery 2008 demonstrating efficacy of pregabalin in older patients with GAD) and recommends pregabalin and any further evidence-based treatments for elderly patients with GAD.*	
133	SH	Pfizer Ltd.	NICE	1.2.41	20 -21	[Also FULL version 8.6: 272-278] Section 1.2.41 (NICE version) states that "evidence for the effectiveness of combination treatments is lacking" in patients with complex, treatment-refractory GAD. *However, a study demonstrating the efficacy of add-on pregabalin in treatment-refractory patients has not been included in the guideline (Miceli 2009).* In this study, GAD patients who did not respond to a course of an SSRI or an SNRI or a benzodiazepine, and had only a partial response with a different SSRI or SNRI were randomised to receive add-on pregabalin or placebo to continued use of SSRI/SNRI treatment. 353 patients were randomized and treated with adjunctive pregabalin (n=177; mean baseline HAM-A, 20.7) or placebo (n=176; mean baseline HAM-A, 21.4). For the primary analysis, the mean (SE) change in HAM-A was significantly greater for pregabalin compared to placebo (–7.74 [0.38] vs –6.55 [0.38]; difference score, –1.19 [adjusted 95% CI: –2.14 to –0.24]; P<0.05). At week 8, HAM-A responder rates (≥50% reduction) were significantly higher on adjunctive pregabalin compared to placebo (50% vs 37%; P=0.023).Treatment with pregabalin was associated with a significantly earlier time-to-sustained response compared to placebo (log-rank P=0.014). This information comes from the poster presented at the APA congress 2009, which has been	Thank you for your comment. We cannot consider conference abstracts and can only consider full trial reports so that we have enough details to do a comprehensive quality assessment.

						provided by Pfizer along with this response. *In contrast to this study demonstrating statistically significant results for add-on pregabalin compared to placebo, the meta-analysis results for other augmentation strategies (adding antipsychotics to pharmacological treatment for GAD or AD) were not found to be statistically significant (page 277, full guideline).* *It seems that this study was missed from the guideline as it is currently only available as an abstract, and it seems that the National Collaborating Centre did not search for relevant conference abstracts (section 8.6.2, full guideline). This is a significant omission given the high quality and large sample size of this new trial in comparison to the current lack of robust data in this refractory GAD population (as recognised by the current guideline).* *We recommend that pregabalin is mentioned as a treatment option for treatment-refractory patients with GAD in section 1.2.41 (NICE version).* Please see below our recommended changes to section 1.2.41 in bold text: "Consider offering combinations of psychological and drug treatments, combinations of antidepressants or augmentation of antidepressants with other drugs **(e.g. pregabalin)**, but exercise caution and be aware that: • **With the exception of pregabalin,** evidence for the effectiveness of combination treatments is lacking, and * side effects and interactions are more likely when combining and augmenting antidepressants. [new 2011]	
134	SH	Pfizer Ltd.	Full	8.8.2	296	There appears to be a cost error in the economic model for pregabalin (*Table* 68, page 296). It	Thank you very much for spotting this error. We have corrected the cost estimate, to

						seems that the cost for pregabalin has been calculated on a once-a-day basis, but pregabalin is only licensed for twice or three times daily use. However, we would recommend that pregabalin is prescribed and costed as a twice daily therapy, as the evidence shows that twice-daily dosing is as efficacious as thrice-daily. dosing (Pohl 2005), and there are likely to be adherence and cost benefits.	include two doses of 150mg per day (300mg per day in total).
135	SH	Pfizer Ltd.	Full	General	General	Studies cited: Baldwin DS, Anderson IM, Nutt DJ, Bandelow B et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology Journal of Psychopharmacology 2005; 19 (6): 567–596 Bandelow, Borwin, Zohar, Joseph, Hollander, Eric, Kasper, Siegfried, Möller, Hans-Jürgen and WFSBP Task Force On Treatment Guidelines For Anxiety Obsessive-Compulsive Post-Traumatic Stress Disorders(2008) 'World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders - First Revision',World Journal of Biological Psychiatry,9:4,248 — 312 Beekman ATF, Bremmer MA, Deeg DJH, Van Balkom AJLM, Smit JH, De Beurs E ,Van Dyck R, and Van Tilburg W Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam Int. J. Geriat. Psychiatry 13, 717-726 (1998) Flint AJ. 1994. Epidemiology and comorbidity of anxiety disorders in the elderly. Am J Psychiatry 151(5): 640–649.	Thank you for your comment.

						Kasper S, Herman B, Nivoli G, Van Ameringen M, Petralia A, Mandel FS, et al. Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind, placebo-controlled 8-week trial. Int Clin Psychopharmacol 2009 ; 24(2):87-96 Kavoussi, R. (2006) Pregabalin: from molecule to medicine. European Neuropsychopharmacology, 16, S128-S133. Miceli JJ, Ramey TS, Weaver JJ, Gleit JA, Knapp L. Adjunctive pregabalin treatment after partial response in generalized anxiety disorder: Results of a Double-Blind Placebo Controlled trial. Presented at the 162nd Annual Meeting of the American Psychiatric Association. May 16-21, 2009, San Francisco, USA Montgomery S Pregabalin for the treatment of generalised anxiety disorder. Expert Opin. Pharmacother 2006: 7(15): 2139 – 2154 Montgomery S, Chatamra K, Pauer L, Whalen E, Baldinetti F. Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder. Br J Psychiatry 2008;193(5):389-94. Pohl RB, Feltner DE, Fieve RR, and Pande AC Efficacy of Pregabalin in the Treatment of Generalized Anxiety Disorder Double-blind, Placebo-Controlled Comparison of BID versus TID Dosing J Clin Psychopharmacol 2005;25:151–158 Schoevers RA, Beekman ATF, Deeg DJH., Jonker C and van Tilburg W. Comorbidity and risk-patterns of depression, generalised anxiety disorder and mixed anxiety-depression in later life: results from the AMSTEL study Int J Geriatr Psychiatry 2003; 18: 994–1001	

						 miceli-poster2009.pdf	
136	SH	Royal College of General Practitioners, Wales	NICE	General	General	It is sensible that this guideline uses DSM-IV rather than ICD-10 criteria to define the diagnosis of GAD and panic disorder. This makes treatment options more understandable and comparable	Thank you for your comment
137	SH	Royal College of General Practitioners, Wales	NICE	General	General	Good communication between practitioners and people with generalised anxiety disorder or panic disorder is essential but often difficult to ensure due to time limitations and the lack of available resources for referral.	Thank you for your comment. We acknowledge the multiple competing demands on practitioners' time and difficult judgements they have to make about how best to use their time and also the variability in referral resources in different parts of England and Wales.
138	SH	Royal College of General Practitioners, Wales	NICE	KPIs	7	It is easy to Provide the person with verbal information on the likely benefits and disadvantages of each mode of treatment, but giving written information depends on available technology as it is impossible to keep a Library of all required information. A suggestion may be to develop an online library of useful leaflets.	Thank you for your comment. All NICE guidelines and 'Understanding NICE guidance', the documents for service users are available to download from the NICE website in PDF and Word format. www.nice.org
139	SH	Royal College of General Practitioners, Wales	NICE	1.2.1	10	The stepped care model is easy to follow and understand	Thank you for your comment
140	SH	Royal College of General Practitioners, Wales	NICE	1.2.2	16	It is useful to have clear statement re preferred treatments. If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI).	Thank you. This has now been changed in the light of other comments – we now say offer an SSRI, and consider offering sertraline first on grounds of it being clearly the most cost effective.
141	SH	Royal College of General Practitioners, Wales	NICE	1.2.42	21	Combination treatments should be undertaken only by practitioners with expertise in the psychological and drug treatment of complex, treatment-refractory anxiety disorders and after full discussion with the person about the likely advantages and disadvantages of the treatments suggested. It is vital that this is understood by service	Thank you for your comment, we agree that all treatments should be undertaken by appropriately trained healthcare professionals.

						providers and that the expectation that all can be provided in primary care is refuted.	
142	SH	Royal College of General Practitioners, Wales	NICE	4.1	36	We would be keen to see a properly conducted randomised trial to clarify whether sertraline or CBT are most efficacious in the treatment of GAD	Thank you for your comment
143	SH	Royal College of General Practitioners, Wales	NICE	4.2	37	We would be keen to see a trial to establish whether CCBT is an effective alternative to therapist-delivered CBT and one that should be provided.	Thank you for your comment
144	SH	Royal College of General Practitioners, Wales	NICE	4.5	39	Although in theory – keen to support the idea that GPs in intervention practices should receive training in recognising GAD and providing both drug treatment and GP-delivered low-intensity psychological interventions (psychoeducation and pure self-help). The time and training requirements may outweigh potential benefits to the smooth running of Practices	Thank you for your comment. The recommendations in the guideline are based on the evidence reviewed. Implementation of the recommendations should be dealt with locally.
145	SH	Royal College of Nursing	All	General	General	This organisation responded with no comments to make	Thank you.
146	SH	Royal Pharmaceutical Society of GB	Full	General	General	The RPSGB welcomes these guidelines	Thank you for your comment
147	SH	Royal Pharmaceutical Society of GB	Full	8	306 -311	If the recommendations for pharmacological interventions are accepted there will need to be substantial amendments to the guidance on Anxiolytics contained in the BNF in relation to the choice and general use of Beta Blockers, antipsychotics, antidepressants and Benzodiazepines.	Thank you for your comments. The guidance relates to the management of GAD which is a specific anxiety disorder while the advice in the BNF relates to anxiety in general and would include many conditions in primary care which do not meet criteria for GAD. The BNF does not include antidepressants as anxiolytics and their advice in this respect could be usefully updated. The recommendations we have made are based upon the best evidence for cost effectiveness for drugs in the treatment of GAD, rather than anxiety more broadly**.**
148	SH	Sheffield Health and Social Care Trust	All	General	General	There is no specific reference to the role of specialist psychological or psychotherapy services. We have good case examples of joint working with liaison services to offer rapid access to experienced therapists, which evidence the role of the multi-disciplinary/ multi-modal	Thank you for your comment. We have clarified that Step 4 includes specialist services, which may include specialist psychological therapy services.

						psychotherapy services. I recently re-evaluated, with my colleagues, a past collaboration that looked at the reduction in the use of sedation with dentally anxious patients and we found that the effect of therapy endured in 68% of the cases after 10 years. The patients, in effect, had not returned to the use of sedation to deal with their anxiety (submitted for publication in 2010). The role of these services, as specialist services, appears to have been ignored at Step 5.	
149	SH	Sheffield Health and Social Care Trust	All	General	General	Since the inception of IAPT, our experience has been that there are patients who are now being referred who do not necessarily require the full benefits of a CMHT, but require a more comprehensive specialist intervention from experienced therapists offering a psychological therapy pathway. I would be happy to submit case examples.	Thank you for your comment. We have modified the recommendations about specialist interventions at Step 4 so they no longer specify that they are only delivered in multiprofessional secondary care services; they may be delivered in different service configurations and settings.
150	SH	Sheffield Health and Social Care Trust	All	General	General	Multi-modal therapy services offering more than just CBT do not appear to be recommended. We have good case examples of working multi-modally and this is congruent with past evidence, particularly when CBT fails.	Thank you, we have systematically searched for all psychological therapy studies. Case examples do not meet the methodology criteria in our review protocol. Complex, treatment refractory GAD with marked functional impairment is covered in Step 4 of the guideline
151	SH	Sheffield Health and Social Care Trust	All	General	General	There is no acknowledgement of specialist services for the patient who has trans-diagnostic problems. Most patients who get to level 5 will be in this position, but the guideline appears to not acknowledge this fact. This appears to be the profile of patients we see at a tertiary level.	Thank you for your comment. The introduction to the guideline makes clear that pure GAD is rare; the majority of people with GAD have other comorbid mental health problems. While the guideline suggests that most people with GAD will be adequately treated at Steps 2 and 3, and at Step 3 CBT for GAD may well include trans-diagnostic approaches, some people with complex treatment-refractory GAD and marked functional impairment will require treatment from specialist services. Such specialist services are likely to be seeing people with a range of diagnoses and comorbid problems.
152	SH	Welsh Assembly Government	All	General	General	This organisation responded with no comments to make	Thank you.

153	PR	Dr David Baldwin		General	General	I have reservations about the inclusion of GAD and panic disorder within the same guidance. Whilst they share some common aspects, the two conditions differ in their clinical features, epidemiology, presumed neuropsychobiology and genetic-developmental-social origins, and treatment response. Considering them together is akin to considering the management of unipolar and bipolar depression within the same guidance. NICE regards it as being sensible to consider obsessive-compulsive disorder and post-traumatic stress disorder separately and I do not understand why this stance was not taken for GAD and panic disorder. Considering the two conditions together makes the guidance more complex for clinicians to understand and presumably would reduce the likelihood of widespread endorsement and incorporation into clinical practice.	Thank you for your comment. We were not asked by NICE to update the full clinical guideline for panic disorder and therefore were only able to partially update it. We would encourage you to take up any issues regarding methodology with NICE directly.
154	PR	Dr David Baldwin		8		The recommendation for use of sertraline as a first-line pharmacological treatment has some justification, as it has proven placebo-controlled evidence of efficacy in acute treatment of GAD. However, there is no published placebo-controlled evidence of its efficacy in relapse prevention in GAD, and the lack of data establishing its maintenance of effect presumably underlies the fact that it has not been granted a marketing authorisation for the condition. There is an internal inconsistency within the guidance, as when considering panic disorder the recommendation for pharmacological treatment is for a 'licensed SSRI', whereas the recommendation for GAD is for an SSRI which has insufficient supporting evidence for a product licence. It cannot be assumed that sertraline is necessarily efficacious in preventing relapse in GAD, based on knowledge that some other SSRIs (paroxetine, escitalopram) are beneficial: as the formal relapse prevention trial with venlafaxine in GAD did not find evidence that it was efficacious in preventing	Thank you. We agree that there is no evidence assessing the efficacy of sertraline for relapse prevention in GAD. But on the basis of our current knowledge of the published literature there appears to be strong evidence across anxiety disorders that SSRIs are effective for relapse prevention (Donovan *et al.,* 2010). In our systematic review we did not identify any formal relapse prevention trials on venlafaxine for GAD although we would be interested in further information if such a trial has been undertaken. In addition, we have no evidence to suggest that a lack of efficacy in relation to relapse prevention was the reason sertraline has not obtained market authorization. It is also important to note that the economic analysis showed that sertraline was by far the most cost-effective pharmacological treatment option.

						relapse.	
155	PR	Dr David Baldwin		8		In many places, the guidance states that benzodiazepines should not be used in primary or secondary care, for either GAD or panic disorder, given their undoubted tolerability problems and potential for dependence and withdrawal syndromes. This is not especially contentious, but it could be argued that there is still a role for use of benzodiazepines in situations other than a 'short-term measure during crises': for example, in tertiary care settings, where a patient has not responded to a series of interventions (including CBT, SSRI, SNRI and pregabalin treatment) and remains troubled by severe, distressing and disabling symptoms.	Thank you for your comment. The scope for this guideline restricts us to making recommendations for primary and secondary care. If a patient has reached tertiary care, clinicians working in primary and secondary care will have already exhausted the measures recommended in this guideline. At this stage, the weak empirical evidence for the use of benzodiazepines will be overshadowed by the experience of the specialist treating them, who may feel that benzodiazepines should be prescribed in specific cases.
156	PR	Dr David Baldwin	NICE	Introduction	4	The current requirement for a 6-month duration of symptoms for the diagnosis of GAD is likely to change to a 3-month duration in DSM-5. Community studies that employ a 1-month, 3-month or 6-month duration criterion find little difference in outcome and comorbidity, so it might be worth mentioning that symptoms 'should have been present for at least a few months'.	Thank you for this suggestion. We reference some of the studies on duration of symptoms in the Introduction to the Full Guideline. We considered whether to include duration of symptoms of under 6 months as subclinical cases of GAD but decided against this because of the lack of any intervention trials with such cases. The section you make this comment about describes the DSM-IV diagnostic criteria for GAD. As stated in the Introduction to the Full Guideline, in line with the previous anxiety guideline and other NICE guidelines for anxiety disorders and depression, we have used DSM-IV to define the diagnosis of GAD, because the evidence base for interventions nearly always uses DSM-IV.
157	PR	Dr David Baldwin	NICE	Introduction	5	When considering the need for treatment, I suggest that 'symptom severity' is added to the existing list of duration, degree of distress, functional impairment, personal past history and diagnostic comorbidities.	Thank you for the suggestion which we have incorporated into the revision.
158	PR	Dr David Baldwin	NICE	KPIs		Key priorities for implementation. The use of the word 'pure' seems odd, when describing self-help that is not guided by others: how about just using 'individual self-help'.	Thank you for your comment. The GDG has taken your comment into consideration and changed 'pure self-help' to 'non-facilitated self-help', as the group felt that this term would be

							most easily recognised by clinicians.
159	PR	Dr David Baldwin	NICE	1.1.1		The recommendation to 'explore empathically all of the person's worries' is laudable but I found myself wondering how feasible that was in clinical practice and whether it was necessarily in the patient's best interests, when limited time could be used in the other aspects of management.	Thank you for your comment. We have amended the wording of the recommendation to reflect your concerns.
160	PR	Dr David Baldwin	NICE	1.2.16		As there is indeed 'no evidence that either mode of treatment is better' the wording here seems a little unbalanced, when stressing that clinicians should emphasise the 'tendency of drug treatments to be associated with side effects and withdrawal syndromes', whilst not also mentioning potential problems with psychological interventions such as the time commitment and potential for dependence on the therapist.	Thank you for your comment. We agree there are benefits and disadvantages for both drug treatments and psychological interventions as stated in the recommendation. The specific issue of side effects and withdrawal symptoms was used only as an example and the guideline development considered that using too many examples would make the recommendation overly long. The recommendation clearly states the choice of treatment is based on patient preference – so we do not think that it is unbalanced in favour of either intervention.
161	PR	Dr David Baldwin	NICE	1.2		Step 4 in the Stepped Care Model refers to 'highly specialist treatment' but the locus of this stage of management is in secondary care settings. I do not believe that treatment strategies such as dosage adjustment or combination approaches should be regarded as highly specialist interventions.	Thank you for this comment. Dosage adjustment, switching of drugs and combined pharmacological and psychological treatment we have indicated are at Step 3. We were advised combination drug treatments are outwith the expertise of most GPs and this has been confirmed by stakeholder comments from GP professional bodies. However, we have altered the wording of the recommendations about Step 4 specialist interventions so that these are not limited to being provided in secondary care.
162	PR	Dr David Baldwin	NICE	1.2.8		The recommendation here is that patients with GAD combined with harmful and dependent alcohol misuse should first undergo treatment for alcohol misuse, 'as this alone may lead to significant improvement in the symptoms of GAD': this is true for some patients, but many will require simultaneous management of the two conditions and I suggest the wording is adjusted.	Thank you for your comment. The thrust of the full recommendation 1.2.8 is that alcohol misuse should not be a contraindication to treatment of GAD, but where there is more serious, harmful or dependent alcohol misuse, the alcohol misuse should be treated first. We acknowledge that some people with GAD and comorbid harmful or dependent alcohol misuse

							will go on to need consecutive or concurrent treatment for GAD, but consider that the recommendation to start treatment for alcohol misuse first is appropriate. It is also in line with the recommendations of the NICE guideline being developed on the management of alcohol dependence and harmful alcohol use which has also been out for consultation at the same time as this guideline.
163	PR	Dr David Baldwin	NICE	1.2.8	15	The recommendation that practitioners use 'routine outcome measures' is clearly sensible but it would be worth naming some measures here, based on proven validity, reliability, sensitivity and feasibility in practice.	Thank you for your comment. The choice of a routine outcome measure will reflect different practitioners' working contexts, depending on whether a measure or measures to cover a range of common mental health disorders is needed or a disorder specific measure. Also a review of validity of measures for GAD was not within the scope of the guideline. Accordingly we shall not be adding specific recommendations of measures.
164	PR	Dr David Baldwin	NICE	1.2.22		Sertraline is mentioned as the most cost-effective drug treatment (based on the analysis undertaken for the Group), but I suggest it should be stated here that it is not licensed for the treatment of patients with GAD.	Thank you for your comment, this recommendation already includes the statement that sertraline is not licensed for GAD (in the footnote).
165	PR	Dr David Baldwin	NICE	1.2.23	16	The list of bullet points of factors to be considered when sertraline is ineffective should include the potential for drug-drug interactions, which is important for paroxetine and venlafaxine.	Thank you for your comment. We have amended the recommendation in the light of your comment.
166	PR	Dr David Baldwin	NICE	1.2.24		recommendation that pregabalin should be preferred to an SNRI, when a patient has not been able to tolerate an SSRI is an approach that is commonly used in clinical practice but the statement needs to be expanded.	Thank you for your comment. The recommendation has been amended, although it is not usually NICE policy to provide a rationale for recommendations unless the advice will be a major change to clinical practice. The justification for this recommendation can be found in the full guideline.
167	PR	Dr David Baldwin	NICE	1.2.30	18	The guidance on what to do, should a patient develop side effects soon after starting drug treatment does not include consideration of reducing the dosage, but this is possible for most	Thank you for this suggestion which we have added to one of the bullet points.

						of the drugs that are licensed for GAD.	
168	PR	Dr David Baldwin	NICE	1.2.37	20	The list of bullet points describing 'Assessment' in secondary care (Step 4) does not include asking about adherence to previously prescribed pharmacological treatments or fidelity to prior psychological interventions.	Thank you for your comment. We have amended the recommendation in light of your concerns.
169	PR	Dr David Baldwin	NICE		25	Page 25. Presentation in A&E with panic attacks. The wording should perhaps be altered to 'It is important to remember that a panic attack does not ~~necessarily~~ constitute ~~a~~ panic disorder…'.	Thank you for your comment. This section on panic was not updated as part of the current review, therefore the original wording from the 2004 version stands.
170	PR	Dr David Baldwin	NICE	1.4.20	28	The statement that 'the two classes of antidepressant that have an evidence base for effectiveness' are the SSRIs and TCAs is contentious: the SNRI venlafaxine has proven efficacy in both acute and continuation treatment in panic disorder.	Thank you for your comment. This section on panic was not updated as part of the current review, therefore we are not able to review or revised sections on panic disorder (besides CCBT).
171	PR	Dr David Baldwin	NICE	1.4.26	29	The recommendation that 'in some instances' doses at the upper end of the indicated dose range may be necessary (for antidepressant treatment in panic disorder) suggests that this is an uncommon likelihood, but it should be remembered that fixed-dose studies with paroxetine and citalopram suggest that higher doses may be more efficacious, and that flexible-dose studies often find that the mean dosage at study end-point is towards the high end of the dosage range.	Thank you for your comment. This section on panic was not updated as part of the current review, therefore we are not able to review or revised sections on panic disorder (besides cCBT).
172	PR	Dr David Baldwin	NICE	1.4.30	30	Typographic error: 'doss' (presumably, 'doses').	Thank you for your comment, we have corrected this.
173	PR	Dr David Baldwin	NICE		35	Some of the suggested areas for research stipulate the measures for assessing response to interventions – for example of 50% or greater reduction in symptom severity on the HAMA scale (response) or a HAMA score of 7 or less (remission) – but others do not, and it might be helpful to make the same recommendations for assessing outcome throughout this section.	Thank you for your comment. This has been discussed at the GDG meetings and we believe naming one or two specific outcome measures may not be helpful as research context differs. Instead, we altered the wording to outcomes *specific to GAD* in all research recommendations. We have also applied this wording to all research recommendations for consistency.
174	PR	Professor Adrian Wells	Full	genera l	general	The panel should be commended on a thorough and well structured appraisal of the research	Thank you for your comment.

175	PR	Professor Adrian Wells	Full	general	general	The analysis of outcomes for psychological therapies uses CBT and AR as generic categories for amalgamating studies. This is based on the unsafe assumption that different CBT's produce equivalent effects and that different AR's produce equivalent effects or target the same mechanisms. The variance in outcomes for AR is large and recent studies (Wells 2010) suggest metacognitive therapy is superior to AR, and in a large RCT metacognitive therapy was superior to another form of CBT (van der Heiden et al, submitted—) There may now be a significant loss of data in having a generic CBT category in the same way that it would not be advisable to have a generic 'antidepressant treatment' but to separate different drugs in this group. More recent forms of CBT are based on specific conceptualizations of worry and target specific underlying mechanisms. They may produce stronger effects than the earlier CBT's (see clinical significance analysis by Fisher 2006- The efficacy of psychological treatments for generalised anxiety disorder. In G. Davey & A Wells eds; Worry and its psychological disorders. Chichester, UK Wiley, Ch. 20 pp 359-377, and Wells et al 2010, and van der Heiden, submitted). The amalgamation of treatments into a generic CBT category obscures important differences in effects and their implications for treatment and future research recommendations. I recommend inclusion of the large scale van der Heiden study and an additional sub-sample analysis reflecting the possible differences in CBT types and/or acknowledgment that differences between treatments have been reported in some analyses but these might be obscured by aggregating treatment modalities. Another possibility would be to remove the MCT trial from the overall analysis and report these narratively as an example of treatment not fully conforming to	Thanks for your comment. We do acknowledge the different types of CBT and that these may produce different effects. A sub-sample/sensitivity analysis has been added and we highlighted the difference in effects on three outcome measures. All other outcomes remained robust. Note that there are no statistically significant findings from the sensitivity analysis that would change our recommendations.

						earlier CBT's because they target specific worry mechanisms rather than the content of worry.	
176	PR	Professor Adrian Wells	Full	general	general	The outcomes assessed rely largely on somatic/arousal based anxiety measures, but the index of effects should be moved towards assessing the effects on worry as this is the central feature of GAD and will figure more prominently in DSM V. Where possible treatment effects should be compared on the Penn State worry questionnaire and/or the Trait-anxiety subscale. The use of more somatic measures is less sensitive especially in detecting possible differences in effects produced by the more recent treatments that actively target worry.	Thank you for your comment. We used Penn State Worry Questionnaire as the measure for Worry where reported in studies, and Beck Anxiety Inventory or State-Trait-Anxiety Inventory as the measure of self-rated anxiety scores. Studies of pharmacological interventions usually just reported clinician rated anxiety on the Hamilton Anxiety Scale. Outcomes extracted from each study are reported in the appendix of our full guideline.
177	PR	Professor Adrian Wells	Full	2.3	23	Apparent contradiction here. Previously stated that GAD responds to placebo and non-specific treatment factors, yet goes on to state that it is difficult to treat with psychological approaches.	Thank you for your comment. We have modified section 2.4.5, which we hope has clarified this issue.
178	PR	Professor Adrian Wells	Full	4.4.3	73	Line 16: The panel might consider including recent findings that the topological features of worry do not distinguish high worriers without GAD from those with GAD, but the GAD group can be distinguished on the basis of negative beliefs about worrying (Ruscio & Borkovec, 2004- Experience and appraisal of worry among high worriers with and without generalized anxiety disorder. Behaviour Research and Therapy, 42, 1469-1482)	Thank you. A paragraph has been added to reflect these findings, see section 4.4.3.
179	PR	Professor Adrian Wells	Full		95 & 106	Inconsistency: on p95 it is suggested that Applied Relaxation (AR) is used as a high-intensity intervention but on p106 suggested that it is used in low intensity. AR requires adherence to stages in a manual and correct application using a tailored rationale. It is better suited to high intensity rather than low intensity delivery.	The Applied Relaxation referred in high intensity chapter is different from the relaxation training in low intensity chapter. We do understand the confusion. The naming of the relaxation training in low intensity chapter has been changed accordingly.
180	PR	Professor Adrian Wells	Full	6.7.2.2	150	Recommendations for further research state that physical activity should be compared with a wait-list. It is not clear why outcome is operationalised in terms of HAM-A scores (this is a non-specific measure of anxiety). Should the example be more GAD specific? (i.e. a worry measure).	Thank you for your comment. This has been discussed at the GDG meetings and we believe naming one or two specific outcome measures may not be helpful as research context differs. Instead, we altered the wording to outcomes *specific to GAD* in all research

						Furthermore, suggestions for outcome measures are not given in the preceding section 6.7.2.1. Consider standardizing recommendations for outcome measures across future research and reflecting assessment of more specific symptoms, namely worry (i.e. PSWQ and Trait-anxiety).	recommendations.
181	PR	Professor Adrian Wells	Full	7	155	Relates to point 2 above. Combining all CBT's possibly blurs important distinctions between the relative effects of psychological treatments and they may not be equally effective.	Thanks for your comment. We do acknowledge the different types of CBT and that these may produce different effects. A sub-sample/sensitivity analysis has been added and we highlighted the difference in effects on three outcome measures. All other outcomes remained robust. Note that there are no statistical significant findings from the sensitivity analysis that would change our recommendations.
182	PR	Professor Adrian Wells	Full		158	The outcomes from (8)Wells et study uses the BAI. However, this is a non-specific measure not especially pertinent to GAD. Outcomes on the PSWQ and the Trait-anxiety subscale are much more meaningful in the context of GAD because they tap worry and apprehension and are available for this study. Choice of least appropriate measures makes interpretation difficult. Analysis should be based on the more appropriate measures for this disorder whenever possible.	We did use PSWQ as a measure of worry. We used BAI as a measure of anxiety (instead of Trait-anxiety subscale) is because BAI was the most commonly reported scale which could be used to compare with other studies.
183	PR	Professor Adrian Wells	Full	5.2	86	In the recognition and assessment of GAD the guidelines would be strengthened by greater emphasis on the necessity for at least 2 worry topics in GAD. The possibility of misdiagnosis is compounded in some of the patient narratives with a predominance of health worry which could lead hypochondriasis to be mis-identified as GAD.	The section on recognition and assessment was not intended to cover standard diagnostic advice regarding identification and diagnosis of GAD as we were not asked by NICE as part of the scope to consider identification and diagnosis; these questions will be included in a NICE guideline on common mental health disorders. We acknowledge that the narratives in Chapter 4 are not exclusively about GAD. Pure GAD accounts would have been ideal, but as GAD is so commonly comorbid with other anxiety disorders and depression the people offering accounts inevitably described

							other anxiety problems in addition to GAD.
184	PR	Professor Adrian Wells	Full	5.2.4	88	The recommendation for assessment should include: Assessing for the presence of a range of different worry topics that have occurred over time or in the current episode.	Thank you for your comment. This recommendation is included at a different place in the guideline (Full Guideline 4.5.6.8; NICE Guideline 1.2.3).
185	PR	Professor Adrian Wells	Full	7.0	153	Applied Relaxation (AR) is entirely attributed to Ost's procedure in the guideline. However, some of the studies reviewed, particularly those conducted by Borkovec use a different form of AR based on the manual of Bernstein and Borkovec. The different types of AR may account for the wider variance in outcomes observed with this technique.	Thanks for your comment. We do acknowledge the different procedures of AR and that these may produce different effects. A sub-sample/sensitivity analysis has been added and we highlighted the difference in effects on one outcome measure. All other outcomes remained robust. Note that there are no statistically significant findings from the sensitivity analysis that would change our recommendations.
186	PR	Professor Adrian Wells	Full	7.3	155	The statistics for the number of trials reviewed do not tally. It is stated that 25 RCT's are identified. That 21 of these compare CBT with WL or other treatment. However the list of studies totals n=27.	Thanks for your comment. Corrections have been made.
187	PR	Professor Adrian Wells	Full	7.3.6	174	A total of 4 trials are used to compare AR with control, active control and other active treatment. I presume this is active treatments other than CBT but this requires clarification.	There were 3 trials comparing AR with waitlist control. And 1 trial comparing AR with non-directive counselling. Please see Table 25 in 7.3.7.
188	PR	Professor Adrian Wells	Full	7.4	191	The list of studies examining the effects of CBT is not consistent with the list in Table 20 (p.158)	Thank you for your comment. Relevant changes have been made.
189	PR	Professor Adrian Wells	NICE	genera l	general	The NICE version may require slight modification of recommendations following implementation of the above.	Thank you for your comment
190	PR	Professor Ian Anderson	Full	Gener al	General	A great improvement on the last guideline.	Thank you for your comment.
191	PR	Professor Ian Anderson	Full	Gener al	General	There is no discussion about suicide in the introduction – it only appears later in the structure of care. There does appear to be an increased risk in GAD which therefore needs some discussion and consideration in assessment (Cougle JR, Keough ME, Riccardi CJ, Sachs-Ericsson N.J. Anxiety disorders and suicidality in the National Comorbidity Survey-Replication. Psychiatr Res. 2009 43(9):825-9. Epub 2009 Jan 14.	Please see section 2.2.3 of the full guideline (line 27).
192	PR	Professor Ian	Full	8.9.1.2	308	I would urge caution in recommending sertraline	Thank you for your suggestion.

		Anderson				as first line so strongly as this is based mainly on only a couple of trials against placebo, there are no longer-term data and prices will inevitably change during the lifetime of this guideline. It may be better tolerated than some other SSRIs (but the Cipriani et al 2009 network analysis suggests this probably not the case against citalopram/escitalopram - although they used total dropouts).	In the last paragraph of the 'Discussion' of the economic model in section 8.8.4 it is already stated that: *"Based on these findings, it is expected that the relative cost effectiveness of drugs for the treatment of GAD is likely to change in the future, as eventually drugs will become available in generic form, resulting in a considerable reduction in their acquisition costs."* We have amended the recommendation in the light of your comments. 'Offer sertraline' has been replaced by 'consider offering sertraline' and we have added the word currently so that it reads *"Consider offering sertraline first because it is the most cost-effective drug".*
193	PR	Professor Ian Anderson	Full	8.9.1.2	308	In addition the footnote that informed consent should be obtained and documented for sertraline is rather vague – for all treatment there should be informed consent. Should this be specifically for off-label use? However the GMC guidance does automatically recommend that. In Good Practice in Prescribing Medicines (2008) http://www.gmc-uk.org/guidance/current/library/prescriptions_faqs.asp it says 'For off-label treatment it may not be necessary to draw attention to the licence where current practice supports it but where patients, or their carers express concern you should explain, in broad terms, the reasons why medicines are not licensed for their proposed use.' Given that NICE are recommending sertraline that supports current practice. While it seems simple to say that it should be explained and consented but in practice it is likely to add time and unnecessary complexity to a consultation where it is not necessary and could possibly be therapeutically counterproductive for some patients.	While we have sympathy with your view that we should always obtain consent for treatment, the GMC and NICE use this form of words in this context. In any event, thank you for your comment.

194	PR	Professor Ian Anderson	Full	8.9.1.3	308	What exactly does 'taking into account the UK market authorisation mean'. Does this mean that it should count for some weight in the decision – how given that a non- authorised drug is recommended first line? If this is to stay could it be clarified because at the moment is simply reads as an exercise in covering one's back.	Thank you. We agree. This has now been omitted from the recommendation.
195	PR	Professor Malcolm Lader	All	General	General	Overall I found the Guidelines on GAD to be very helpful if a little idealistic. Every possible complication can be encountered with respect to diagnosis and treatment. Co-morbidity is the rule rather than the exception. Some of this is not true co-morbidity but a tendency by the patient to present with a range of physical symptoms. Differential diagnosis should be emphasised as many disorders can mimic GAD. One important one is over usage of caffeine, and this can be easily treated.	Thank you for your comment. We have tried to emphasise in the introductory chapter that comorbidity with other mental health problems is the rule rather than the exception, and that somatic presentation as well as comorbidity with physical illness is common. We were not asked by NICE as part of the scope to consider diagnosis and differential diagnosis; this will be included in a NICE guideline on common mental health disorders.
196	PR	Professor Malcolm Lader	All	General	General	I have two general comments first. The diagnosis and treatment of GAD is very much the responsibility of the general practitioner. I think the revised guidelines are too convoluted for GPs and a simpler algorithm might be more appropriate. I am sure you will take into account the views of the GPs that you consult. The second point concerns the ever-present danger of adopting dual standards. My reading of the Guideline, particularly the sections of the full Guideline, leads me to experience some disquiet. Drug treatments seem to be assessed more rigorously than both herbal and non-drug treatments. I have given an example below with camomile. I think the documents should be collated from the detailed database in the full Guideline to the shorter guidelines to ensure that this inconsistency is minimised.	Thank you for your comment, while we accept limitations to the stepped care model presented in the guideline, it was developed in collaboration with GP members of the guideline development group and we have tried to make it as practical as possible for the use of GPs, but at the same time reflect the best available evidence. Thank you for your comment, we agree it is important to use equally rigorous standards when assessing different types of interventions. We have sought to do this, whilst taking into account the different challenges posed in systematically reviewing these interventions.
197	PR	Professor Malcolm Lader	NICE	1.2.11	7	"psychoeducation " Psychojargon! Why not use plain English?	Thank you for your comment. It was agreed by the GDG that 'psychoeducational group' was the most appropriate term as it is in current widespread use.

198	PR	Professor Malcolm Lader	NICE	1.2.16	7	Why not use both according to need and preference? Written information is the more important. GAD patients are too anxious to remember most of what they are told verbally.	Thank you for your comment. It was the GDG's view that the information should be both discussed with the person with GAD and that they should be given written information to take away.
199	PR	Professor Malcolm Lader	NICE	1.2.2	7	This is very important. Making and communicating the diagnosis is very reassuring and starts the therapeutic process.	Thank you for your comment
200	PR	Professor Malcolm Lader	NICE	1.2.3	7	Only a minority of GAD patients present with anxiety; most have somatic complaints	Thank you for your comment. This is an issue we cover in chapter 5 of the Full Guideline and is why this recommendation includes considering the diagnosis of GAD also in people with chronic physical health problems and in people presenting and seeking reassurance about physical symptoms.
201	PR	Professor Malcolm Lader	NICE	1.2.22	8	Sertraline is the choice of Cipriani et al and yet their data strongly favours escitalopram	Thank you for your comment, while we would like to comment on the Cipriani meta-analysis it is not immediately relevant to this guideline as it concerns major depression.
202	PR	Professor Malcolm Lader	NICE	1.2.25	8	With short term use the patient must be told that the benzo will be terminated after a maximum of 4 weeks whatever the response.	Thank you for your comment. The recommendation states that benzodiazepine use should be in line with the BNF, which we think is sufficient.
203	PR	Professor Malcolm Lader	NICE	1.2.26	8	Agreed but see quetiapine data.	Data on quetiapine in the treatment of GAD were not considered at formulation of recommendations, as this is the topic of a future NICE Technology Appraisal.
204	PR	Professor Malcolm Lader	NICE	1.2.36	8	Add alcohol misuse as another reason for referral	Thank you for your comment, we have added alcohol misuse as you have suggested.
205	PR	Professor Malcolm Lader	NICE	1.1.4	10	Very important	Thank you for your comment
206	PR	Professor Malcolm Lader	NICE	1.2.4	12	This takes finesse. Patients are sometimes paranoid for any hint that they are wasting the health care professional's time.	Thank you for drawing attention to this. We agree that this is a difficult issue and we trust that health care professionals will have the clinical acumen and skill in dealing with sensitive situations such as these.
207	PR	Professor Malcolm Lader	NICE	1.2.6	12	Many patients have had previous problems discontinuing medication and are wary of any medication.	Thank you for drawing our attention to this point. We agree that this is a common problem and therefore have highlighted the need for health care professionals to consider 'past experience of, and response to, treatments'

							which include pharmacological treatments and problems that they may encounter with these (1.2.6).
208	PR	Professor Malcolm Lader	NICE	1.2.22	16	Both paroxetine and venlafaxine are associated with frequent withdrawal reactions which can be troublesome and prolong treatment unnecessarily.	Thank you for your comment. We have amended the recommendation in the light of your comment.
209	PR	Professor Malcolm Lader	NICE	1.2.22	18	Sensible advice	Thank you for your comment
210	PR	Professor Malcolm Lader	NICE	1.2.35	19	Essential combination	Thank you for your comment.
211	PR	Professor Malcolm Lader	NICE	1.2.41	21	I think that there is sufficient experience with pregabalin to consider putting it somewhat further up the hierarchy. It is also unlikely to interact strongly with other drugs as it is almost completely excreted through the kidneys.	Thank you for your comment, while we agree pregabalin does not appear to be any less effective or less safe than other pharmacological interventions it was considered very unlikely to be cost-effective.
212	PR	Professor Malcolm Lader	NICE	4.1	36	The design is unbalanced as it has no drug placebo. In addition patients have distinct preferences for drug or non-drug treatments. These should be taken into account	Thank you for your comment, the design does have a waitlist control. Although the GDG considered placebo as a control group they were concerned that it may be ethically difficult to justify randomizing participants to placebo when CBT and sertraline have already been found to be effective treatments. We agree that incorporating participant preference for drug or non-drug treatments would be interesting. However, the GDG concluded this may overcomplicate the trial.
213	PR	Professor Malcolm Lader	NICE	4.3	38	is an uncontrolled study and the results will be uninterpretable	The study design referred in recommendation 4.3 is a randomised controlled trial, which is a controlled study and the results will be interpretable.
214	PR	Professor Malcolm Lader	NICE	4.4	39	I thought the one controlled trial was inconclusive? See page 316 of the full version. The present proposal is premature. Another proof-of-concept study is needed first.	Thank you for your comment. That is correct. The evidence for chamomile is inconclusive as there is only one study. However, there is an indication that this herbal intervention is effective in reducing anxiety and thus a research recommendation for further research in the area is warranted to validate/disconfirm these findings.

Comments on executable models

Response from Lundbeck

Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	Developer's response
Issue 1 **Treatment options assessed in the economic analysis**	Sertraline is included in this economic analysis but: - sertraline is not licensed for the treatment of people with GAD; - evidence on sertraline in GAD is limited compared to other drugs (only two studies are included in the network meta-analysis); - the average of daily dosage for sertraline is assumed to be 100 mg but this assumption is not supported by clinical data or real life evidence.	Two options could be considered to limit uncertainties regarding sertraline in this analysis: 1/ Perform this economic analysis with drugs that are licensed for the treatment of people with GAD only (without sertraline); 2/ Perform a sensitivity analysis considering only drugs that are licensed for the treatment of people with GAD and compare the results with and without sertraline.	Not applicable	Thank you for your suggestion. The GDG reviewed the available clinical evidence and decided to consider sertraline as a potential first line treatment in the economic analysis. No further analyses/scenarios were considered necessary. We provide more details on justification of this decision in the full guideline, and also in our responses to other related comments of yours.
Issue 2 **Side effects**	In this economic analysis, tolerability issues are limited to intolerable side effects and these side effects are estimated at 8 weeks. Therefore, it is considered that side effects can not occur earlier in this decision-tree. Moreover, reduction in utility score due to intolerable side effects was assumed to equal	Suggestion to do the assessment of tolerability issues both in terms of tolerable and intolerable side effects, taking into account that side effects can occur earlier and using reduction in utility score due to side effects for people with GAD.	Not applicable	As we explain in a related comment of yours, the 8-week probability of discontinuation due to intolerable side effects gives the proportion of people that have stopped the drug by the end of 8 weeks – but discontinuation can occur at ANY point within this period. This means that in this decision tree intolerable side effects can actually occur earlier than 8 weeks. According to the GDG expert opinion, most of these discontinuations occur within the first 2 weeks following initiation of treatment, so for purposes of model structure only we assumed that, for people discontinuing, switching to the next drug would occur at the end of 2 weeks from drug initiation. We

	the greatest utility reduction due to side effects reported for people with depression under antidepressant medication			have clarified this point in the final draft. However, probability of people discontinuing due to side effects, as estimated in Network Meta-analysis and utilised in the model, takes into account the total number of people discontinuing from time zero from initiation of treatment, and up to t=8 weeks. No data on reduction in utility due to side effects from medication were identified for people with GAD. The only data available were on reduction of utility due to side effects from antidepressants in people with depression (Revicki and Wood, 1998). This study demonstrated that the reduction in utility was non-significant for most of the side effects from antidepressants. Due to lack of data specific to people with GAD, we decided to use the available data on people with depression. Given the reported insignificance of the impact of most side effects on the HRQoL of people with depression, and the GDG's estimation that intolerable side effects must reduce the HRQoL more considerably compared with tolerable side effects, we decided to consider the impact of intolerable side effects in the HRQoL of people with GAD in the economic analysis. We have explained the rationale for this and have provided details on the respective data used in the economic analysis in the final guideline.
Issue 3 **Cost data**	The number of GP visits is estimated from an expert opinion while in the NICE review of existing models, using such a source resulted in partial acceptance by NICE.	Using real life data (e.g., GPRD) is more appropriate to estimate the number of GP visits in this economic analysis.	Not applicable	Thank you for your comment. Cost data utilised in the model included two different types of costs, as reported in the guideline: a. intervention costs b. other health and social care costs incurred by people with GAD The former, consisted of drug acquisition costs (estimated using the optimal daily dosage for each drug, consistent with data taken from RCTs included in the guideline meta-analysis, and BNF prices) and costs of GP visits. No data on the *optimal* number of GP visits required for pharmacological treatment of people with GAD are available, and therefore we had to use the GDG expert opinion for this model estimate.

				However, in order to estimate the latter, that is, other health and social care costs incurred by people with GAD (*including* GP visits) we did use real resource use data derived from the adult psychiatric morbidity survey in England (McManus et al., 2009), supported by the GDG expert opinion, as reported in the guideline. Please note that, according to NICE guidance for the development of clinical guidelines (NICE, The Guidelines Manual 2009), it is advised that "the health economist should look at pragmatic options for identifying inputs. Examples include using the clinical evidence for that key clinical issue (and perhaps other relevant issues) and liaising with the systematic reviewer, other GDG members and other experts".

Issue 4 **Relapse**	Relapse can occur after response and not after remission that is not in accordance with the standard definition of relapse.	It is suggested to include 'remission' in the model structure and consider 'relapse after remission' according to relapse definition.	Not applicable	The model structure/health states were dictated by the availability of appropriate clinical and utility data considered in the guideline systematic review. The guideline systematic review included data on both response and remission. Utilisation of both types of data was not possible, because not all studies provided data on both outcomes so as to estimate the numbers of people with GAD who responded to treatment but did not meet criteria for remission, and of those who responded to treatment and remitted. For the economic model, it was decided to utilise response (rather remission) data for the following reasons: 1. Response data were available from a larger number of studies, including a higher number of participants; 2. Clinical data on relapse, which were utilised in the model in the form of a 6-month probability of relapse, referred to people who had *responded* to treatment and not to people who had *remitted*. No relapse data following remission were available in the literature covered in the guideline. 3. Utility data were available for the health state of 'response' but not for the health state of 'remission'; in addition, the utility data used in the model, taken from one of the studies that also provided data on relapse following response (Allgulander et al, 2006), referred to the health states of 'relapse following response' and 'no relapse following response' – which were the health states we modelled. No utility values on 'relapse following remission' where identified in the literature. We had added a paragraph in the final guideline text discussing this issue. The model structure did not include a state of 'remission' but rather a state of 'no relapse' at the end of the 6-month maintenance treatment following response, according to availability of clinical and utility data

				considered in the guideline systematic review. It is true that some people who have responded and have subsequently not relapsed in the model may have actually remitted, and they may relapse at a later stage. However, the model did not consider these further stages of the course of GAD, due to lack of appropriate clinical and utility data. The state of 'no relapse following response' is an endpoint of the model. In any case, the rates of relapse following remission are low and definitely much lower than the relapse rates following response (see Yonkers et al, Phenomenology and course of generalised anxiety disorder. Br J Psychiatry 1996; 168: 308-13), which means that non-incorporation of such an event is likely to have had a small impact on the model outcomes.
Issue 5 **Response**	The probability of response is defined in case of no discontinuation due to side effects. However, to calculate these probabilities, individual patient data are required (in order to include patient with discontinuation due to lack of efficacy but exclude patients who discontinued due to tolerability) and these data are not available in all studies included in the network meta-analysis.	More details on the method used to calculate the probability of response and the assumptions that are made when individual data are not available.	Not applicable	The rate of conditional response was estimated as the **number of people in each arm of a trial responding to treatment** divided by the number of **all participants in the arm** excluding **those who discontinued due to side effects**. People who discontinued treatment for *any* reason were considered as non-responders in the guideline meta-analysis, according to ITT (intension-to-treat) approach. All 25 studies included in the network meta-analysis of conditional response provided data on the 3 outcomes highlighted in bold, above. Therefore, it was possible to estimate rates of conditional response from each trial arm included in the network meta-analysis. We have clarified this point in Appendix 14.

These stakeholder organisations were approached but did not respond:

Association for Rational Emotive Behaviour Therapy
Association of British Insurers (ABI)
Association of Dance Movement Therapy UK
Association of Higher Education Programmes on Substance Misuse
AstraZeneca UK Ltd

Berkshire Healthcare NHS Foundation Trust
Birmingham and Solihull Mental Health Foundation Trust
Boehringer Ingelheim Ltd
Bouenemouth University
Bradford District Care Trust
British Acupuncture Council
British Association for Behavioural & Cognitive Psychotherapies (BABCP)
British Association for Psychopharmacology
British Association of Art Therapists
British Association of Drama Therapists
British Association of Psychodrama and Sociodrama (BPA)
British National Formulary (BNF)
British Paediatric Mental Health Group
British Psychodrama Association
British Psychological Society, The
Business Boosters Network CIC
Care Quality Commission (CQC)
Centre for Mental Health Research
Chartered Society of Physiotherapy (CSP)
CIS'ters
Citizens Commission on Human Rights
Cochrane Depression Anxiety & Neurosis Group
College of Occupational Therapists
Commission for Social Care Inspection
Commissioning Support for London
Connecting for Health
County Durham PCT
Department for Communities and Local Government
Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)
Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)
Derbyshire Mental Health Services NHS Trust
Diabetes UK
Faculty of General Dental Practice
Faculty of Occupational Medicine
Faculty of Public Health
Greater Manchester West Mental Health NHS Foundation Trust
Hampshire Partnership NHS Foundation Trust
Health Angels UK Ltd
Hertfordshire Partnership NHS Trust
Humber Mental Health Teaching NHS Trust
Institute of Psychiatry

Intapsych Ltd
Kent & Medway NHS and Social Care Partnership Trust
Lambeth Community Health
Lancashire Care NHS Foundation Trust
Leeds Partnerships NHS Foundation Trust
Leeds PCT
Liverpool Community Health
Liverpool LINk (Local Involvement Network)
Liverpool PCT Provider Services
Manchester Community Health
MBB Connections Healthcare
Medicines and Healthcare Products Regulatory Agency (MHRA)
Mental Health Nurses Association
Mental Health Providers Forum
Mental Heath and Vascular Wellbeing Service
MIND
Ministry of Defence (MoD)
National Association for Children of Alcoholics
National Digital Research Centre
National Offender Management Service
National Patient Safety Agency (NPSA)
National Public Health Service for Wales
National Self Harm Network
NeuroDiversity International(NDI)/NeuroDiversity Self-Advocacy Network(NESAN)
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Isle of Wight
NHS Knowsley
NHS Plus
NHS Quality Improvement Scotland
NHS Sefton
NHS Sheffield
NHS Western Cheshire
North Staffordshire Combined Healthcare NHS Trust
Northern Ireland Chest Heart & Stroke
Northumberland Tyne & Wear Trust
Nottinghamshire Acute Trust
OCD - UK
Offender Health - Department of Health
Oxfordshire & Buckinghamshire Mental Health Partnership NHS Trust
Patients Council
PERIGON Healthcare Ltd

Pharmaceutical Schizophrenia Initiative
Poole and Bournemouth PCT
Positively Pregnant
Pottergate Centre for Dissociation & Trauma
Primary Care Mental Health Forum, RCGP
psc-support
Retreat, The
Royal College of General Practitioners
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Psychiatrists
Royal Society of Medicine
Sainsbury Centre for Mental Health
Salford PCT
Sandwell PCT
SANE
Sanofi-Aventis
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
Social Exclusion Task Force
South Essex Partnership NHS Foundation Trust
South Staffordshire PCT
South West Autistic Rights Movement
South West Yorkshire Partnership NHS Foundation Trust
St Mungos
Sussex Partnership NHS Foundation Trust
Tees Esk & Wear Valleys NHS Trust
Telemedcare Ltd
The British Psychological Society
The Survivors Trust
Tuke Centre, The
United Kingdom Council of Psychotherapists
Welsh Scientific Advisory Committee (WSAC)
West Hertfordshire PCT & East and North Hertfordshire PCT
Western Cheshire PCT
Western Health and Social Care Trust
York NHS Foundation Trust