NICE National Institute for Health and Care Excellence

Cystic fibrosis: diagnosis and management

Consultation on draft guideline - Stakeholder comments table
04/05/17 to 16/06/17

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Organisation name	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Alder Hey Children's NHS Foundation Trust	General		8.3	Excellent to have clear evidence of the incidence of impaired growth in children and young people with CF. This supports the on-going need for specialist dietitians to be involved in the MDT care of children and young people with CF	Thank you for your comment.
Alder Hey Children's NHS Foundation Trust	General		8.7	Excellent to have detailed information on the emerging incidence of CFRD in children and young people with CF. This will help support the case for increasing services for this group	Thank you for your comment.
Alder Hey Children's NHS Foundation Trust	General		10.1	This is an excellent description and summary of the evidence base for nutritional interventions in CF which should enable dietitians to improve nutritional outcome. It is particularly helpful to see enteral tube feeding supported as an intervention	Thank you for your comment.
Alder Hey Children's NHS Foundation Trust	General		10.2	The evidence for specific advice on PERT dosing is very weak but could this be explored further. In my experience effective enzyme dosing to reduce fat malabsorption remains a relatively poorly delivered aspect of CF care	Thank you for your comment. PERT dosing is discussed in the section "Evidence to recommendations" in the full guideline. The committee acknowledged the evidence presented comparing different treatment dosages, but they agreed it was of limited use because it was rated as of very low quality. The committee agreed that evidence regarding the effectiveness of PERT dose in relation to resolution of malabsorption symptoms, improvement in weight and improvement in patient satisfaction or health-related quality of life was very limited and of very low quality or completely lacking. The committee noted that trials were of short duration and therefore it was not possible to assess whether prescribing high dose PERT treatment had an impact on weight. They also noted the dosages used are very low compared to those used in clinical practice. The committee acknowledged that the evidence suggested improved fat absorption with higher doses of pancreatic enzyme replacement therapy. However, dosage was likely to vary on an individual basis since the severity of pancreatic insufficiency was not uniform in people with cystic fibrosis. Optimal dose might differ depending on body size and dietary composition and intake. Infants and young children have a higher intake of fat proportionately than older children, young people and adults. Based on this, the committee agreed to recommend offering PERT to people with cystic fibrosis with pancreatic insufficiency and that the dose should be adjusted for each person in order to minimise symptoms of malabsorption. This recommendation is consistent with clinical practice and aligned with the CF Trust Consensus recommendations (CF Trust, Nutritional Management of Cystic Fibrosis 2016). The committee noted that the normal clinical approach to determining individual need was an empirical one, for instance titrating the PERT dose in terms of units of lipase against the amount of fat being ingested. A standard dose, related to age in children, was usually given and adjustment then made based on the clinical response in terms of trying to achieve a normal bowel habit and the resolution of any malabsorptive symptoms. They agreed that, in people with confirmed pancreatic exocrine insufficiency, the dose should be titrated against symptoms and regularly reviewed. High enzyme concentration products would aid treatment optimisation where there was a higher dose requirement. The committee anticipated that dosing and titration would be done by competent professionals.
Alder Hey Children's NHS Foundation Trust	General	General		Excellent on all aspects of nutritional care and will be extremely helpful evidence both in the nutritional management of children and young people with CF but also in supporting the case for dietetics as an integral part of CF care	Thank you for your comment.
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	Full	172	16	Cost of providing the MDT at the specialist centre. The costs for physiotherapy are based on a Band 7 staff member. However, the Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis Third Edition April 2017 (Cystic Fibrosis Trust publication) state that a CF Specialist Centre must be led by a Principal CF Physiotherapy Practitioner (Band 8). Therefore, we think that the economics for staffing in this guideline should reflect the higher banding and be costed at band 8.	Thank you for your comment. The costing tool has been updated to include one band 8 lead in the specialist centre. A footnote has also been added to the table your comment refers to. The results from that tool have also been updated in the full guideline and appendix k.
Association of Chartered	Full	177	4	CF physiotherapists are also involved in upper airway management. They assess chronic sinus symptoms and teach sinus washouts and use of sinus nebulisation.	Thank you for your comment. We did not review evidence specifically about the role of physiotherapists in upper airway management so are unable to consider including reference to

Physiotherapists in Cystic Fibrosis (ACPCF)					this in the recommendations.
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	Full	231	21	UK CF Registry records prevalence of stress urinary incontinence (question 8.4 UKCF registry document in physiotherapy section)	Thank you for your comment. We looked for UK CF registry data on prevalence of stress urinary incontinence on the CF Trust website however we could not identify this data. The sentence in the full guideline has been amended to state that the UK CF Registry 2015 Annual Data Report did not provide data on prevalence of stress urinary incontinence.
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	Full	231	26	Prevalence studies have been published and we were unsure why these were not included in this section. The reference list is below. White, D., K. Stiller, et al. (2000). "The prevalence and severity of symptoms of incontinence in adult cystic fibrosis patients." Physiotherapy Theory & Practice 16(1): 35-43. Cornacchia, M., A. Zenorini, et al. (2001). "Prevalence of urinary incontinence in women with cystic fibrosis." BJU international 88(1): 44-48. Orr, A., R. J. McVean, et al. (2001). "Questionnaire survey of urinary incontinence in women with cystic fibrosis." British Medical Journal 322(7301). Nixon, M., A. Glazner, et al. (2002). "Urinary incontinence in female adolescents with cystic fibrosis." Pediatrics 110(2). Daniels, Morrison, Lewis 2016 120 Moran, F., J. M. Bradley, et al. (2003). "Incontinence in adult females with cystic fibrosis: a Northern Ireland survey." International journal of clinical practice 57(3): 182-184 Blackwell, K., P. S. J. Malone, et al. (2005). "The prevalence of stress urinary incontinence in patients with cystic fibrosis: An under-recognized problem." Journal of pediatric urology 1(1): 5-9. Prasad, S. A., I. M. Balfour-Lynn, et al. (2006). "A comparison of the prevalence of urinary incontinence in girls with cystic fibrosis, asthma, and healthy controls." Pediatric pulmonology 41(11): 1065-1068. Vella, M., R. Cartwright, et al. (2009). "Prevalence of incontinence and incontinence-specific quality of life impairment in women with cystic fibrosis." Neurourology and urodynamics 28(8): 986-989 .Korzeniewska-Eksterowicz, A., I. Stelmach, et al. (2014). "Urinary incontinence in adolescent females with cystic fibrosis in Poland." Central European Journal of Medicine 9(6): 778-783. Nankivell, G., P. Caldwell, et al. (2010). "Urinary Incontinence in Adolescent Females with Cystic Fibrosis." Paediatric respiratory reviews 11(2): 95-99. Gumery L, Lee J, Whitehouse J et al. (2005) The prevalence of urinary incontinence in adult cystic fibrosis males [abstract] Journal of Cystic Fibrosis 4:S97 Burge, A. T., A. E. Holland, et al. (2011). "Prevalence and impact of incontinence in adult men with cystic fibrosis." Respirology 16.	Thank you for your comment. For the prevalence review on complications of cystic fibrosis, one of the criteria for inclusion was sample size > 250 (please see appendix D for review protocols). The following study was already mentioned in the excluded studies list (appendix H): Blackwell 2005 (Exclusion reason: Sample size <251). The following studies have been assessed as ineligible for inclusion due to sample size <251, however are not mentioned in the list of excluded studies list, because sample size was clear from the abstract and therefore we did not check the full text: Cornacchia 2001, Nixon 2002, Moran 2003, Vella 2009, Korzeniewska-Eksterowicz 2014. The following studies were checked full text based on your comment and were added to the excluded studies list (appendix H): Burge 2011; Orr 2001; Prasad 2006; White 2000 (All these 4 studies were excluded with exclusion reason: sample size <251); Nankivell 2010 (Exclusion reason: literature review); Gumery 2005 (Exclusion reason: Conference abstract. Sample size < 251). Notes have been added next to these studies' references in appendix H indicating that they were identified by stakeholders at consultation. Apologies but it was unclear what "Daniels, Morrison, Lewis 2016 120" refers to. Please note that the flow diagram of clinical article selection in appendix F has now been updated for this review to take into account these additional excluded studies.
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	Full	264	38	Warnock spelt incorrectly	Thank you for your comment. We have corrected the incorrect spelling of Warnock.
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	Full	290	14 - 22	The guideline states that NIV is not widely used in clinical practice. However, it is becoming an established treatment option within the UK and is increasingly not limited to patients using NIV for nocturnal ventilation. The recommendation for use of NIV to support airway clearance techniques (ACT) does not appear to be supported by any published evidence. There is reference to a study (Young 2008) which evaluates the use of NIV for treatment of hypercapnia in which there is no reference to ACT as either a primary or secondary outcome measure. There are other studies which specifically look at this issue and they are included below. We would also refer you to the Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis Third Edition April 2017 (Cystic Fibrosis Trust publication) Moran F et al. Non-invasive ventilation for cystic fibrosis. Cochrane Database Syst Rev. 2013 Apr 30; 4:CD002769. doi: 10.1002/14651858.CD002769.pub4.Review. Pub Med PMID: 23633308. Holland, AE et al. Non-invasive ventilation assistschest physiotherapy in adults with acute exacerbations of cystic fibrosis. Thorax. Oct 2003; vol. 58, no. 10, p.880-884, 0040-6376.	Thank you for your comment. This section of the full guideline has been amended. The sentence stating that NIV is not widely used in clinical practice has now been deleted from the full guideline. The review protocol on airway clearance (appendix D) did not prioritise combinations of interventions, therefore evidence on NIV used as an adjunct to other airway clearance techniques was not assessed for inclusion in the review. As a result, the guideline does not make reference to this, The study by Young (2008) met the protocol criteria because it compared NIV to no intervention (room air). We extracted data from this study on the outcomes outlined in the review protocol for airway clearance (appendix D). Thank you for suggesting these studies. The following Cochrane systematic review was included in the evidence review (please see summary of included studies section in the evidence review): Moran 2013. Moran 2013 was used to extract data on Young 2008. The following studies were excluded from the evidence review (please see Appendix H): Holland 2003 (Exclusion reason: The comparison ACBT vs ACBT and NIV not included in protocol); Faroux 1999 (Exclusion reason: Inspiratory pressure support ventilation (PSV) not included in protocol); Dwyer 2015 (Exclusion reason: Intervention not prioritised for inclusion in the protocol (NIV as adjunct to

				Placidi G et al. Chest physiotherapy with positive airway pressure: a pilot study of short-term effects on sputum clearance in patients with cystic fibrosis and severe airway obstruction. Respiratory Care. 01 October 2006; vol./is. 51/10(1145-1153), 00201324. Fauroux B et al. Chest physiotherapy in cystic fibrosis: improved tolerance with nasal pressure support ventilation. Pediatrics. Mar 1999; vol. 103, no. 3, p. E32. Dwyer TJ et al. Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial. Journal of Physiotherapy. 01 July 2015; vol./is. 61/3 (142-147), 18369553. Stanford, G et al. Positive pressure – analysing the effect of the addition of non-invasive ventilation (NIV) to home airway clearance techniques (ACT) in adult cystic fibrosis (CF) patients. Physiotherapy Theory & Practice. 01 May 2015; vol./is. 31/4(270-274), 09593985. We feel that this section is not fully representative and therefore not entirely accurate. Regarding use of NIV to support ACT – it could be suggested that symptoms associated with reduced oxygen levels may be addressed with the application of controlled oxygen therapy to support ACT in the first instance with NIV therapy trial where indicated to address hypercapnia and hypoventilation.	airway clearance treatments)). Placidi 2006 was included in the review but data was not extracted for the comparison NIV versus control because the control was directed cough, which was not in the protocol. The study by Stanford (2015) was not considered eligible for the review because it evaluates the combination of ACT with NIV and it is a mixed methods study which includes both an uncontrolled before-and-after comparison (not in protocol) and qualitative data (not in protocol). Stanford 2015 does not appear in the list of excluded studies (appendix H) because it was clear from the abstract that it was not relevant so we did not look at the full text. Based on their experience and expertise, the committee noted that NIV could be used in people with cystic fibrosis who have moderate or severe lung disease and cannot clear their lungs using standard airway clearance techniques. The recommendation on NIV has been modified accordingly. With regards to the rationale for the amended recommendation, the full guideline now explains that NIV unloads the respiratory muscles, therefore, it reduces the symptoms associated with respiratory muscle fatigue in moderate and severe lung disease such as reduced oxygen and breathlessness. The Committee also agreed that NIV can be beneficial as a short-term option in moderate disease, when people have difficulty clearing their airways using other clearance techniques, by unloading the respiratory muscles and reducing fatigue. With regards to oxygen therapy, the committee discussed your comment and noted that oxygen therapy alone while correcting oxygen levels will not unload the respiratory muscles and therefore allow better airway clearance and longer clearance sessions through the reduction of fatigue. The committee members noted that they would of course use oxygen for desaturation alone however, they would add NIV if patients were tiring or not achieving sufficient chest clearance with standard airway clearance techniques. The committee decided not to add this discussion on oxygen therapy to the full guideline because oxygen therapy was not included in the review protocol on airway clearance and was not included in the recommendations either.
Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)	Full	292	8	We agree that the vest should not be offered as a first line airway clearance technique but are concerned that the recommendation states that it should never been used. There are instances where it is beneficial and these have been laid out in the Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis Third Edition April 2017 (Cystic Fibrosis Trust publication) • High Frequency Chest Wall Oscillation could be considered when adherence with other airway clearance techniques is problematic • High Frequency Chest Wall Oscillation should be considered when patients are unable to carry out other airway clearance techniques for reasons such as autism, learning difficulties • High Frequency Chest Wall Oscillation could be considered for use in conjunction with other airway clearance techniques eg. Active Cycle of Breathing Technique, PEP mask. If the recommendation is published as it is currently written, it will limit physiotherapists' ability to offer appropriate treatment in some cases. We feel that it should be allowed in particular circumstances as outlined above	Thank you for your comment. The recommendation has been amended to consider the use of high frequency chest wall oscillation in exceptional clinical circumstances as determined by the specialist CF team and following the NHS England policy in individual funding requests. The full guideline explains that the CF team would use the NHS England definition of exceptional clinical circumstances. The committee also discussed your comment about adherence and concluded that unless adherence is problematic due to exceptional clinical circumstances, the CF multi-disciplinary team should work with the person to improve adherence rather than offering high frequency chest wall oscillation. The reasons for not offering high frequency chest wall oscillation except in exceptional clinical circumstances are provided in the full guideline.
British Infection Association	Full	General		*Haemophilus influenzae* is spelled incorrectly with capital and italic formats incorrect throughout. Many other microorganisms (such as *Pseudomonas*) are interchangeably spelled with italics or not or small letters or capitals.	Thank you for your comment. We have ensured there is consistency when referring to Latin names of organisms to ensure they are compliant with NICE Style Guide. They are italicised and start with a capital letter. The genus names then abbreviated after first use in the full guideline but not in the short guideline where recommendations can be read as stand-alone recommendations so it was not felt appropriate to use abbreviations.
British Infection Association	Full	General		As an organisation we support the principals of the full and draft guideline	Thank you for your comment.
British Infection Association	General	General		Microorganisms are spelt incorrectly with capital and small letters in the incorrect locations and no italics in the draft document	Thank you for your comment. We have ensured there is consistency when referring to Latin names of organisms to ensure they are compliant with NICE Style Guide. They are italicised and start with a capital letter. The genus name is then abbreviated after first use in the full guideline but not in the short guideline where recommendations can be read as stand-alone recommendations so it was not felt appropriate to use abbreviations.
British Thoracic Society	Full	231	21	UK CF Registry records prevalence of stress urinary incontinence (question 8.4 UKCF registry document in physiotherapy section)	Thank you for your comment. We looked for UK CF registry data on prevalence of stress urinary incontinence on the CF Trust website however we could not identify this data. The sentence in the full guideline has been amended to state that the UK CF Registry 2015 Annual Data Report did not provide data on prevalence of stress urinary incontinence.
British Thoracic Society	Full	231	26	Prevalence studies published: White, D., K. Stiller, et al. (2000). "The prevalence and severity of symptoms of incontinence in adult cystic fibrosis patients." Physiotherapy Theory & Practice 16(1): 35-43. Cornacchia, M., A. Zenorini, et al. (2001). "Prevalence of urinary incontinence in women with cystic fibrosis." BJU international 88(1): 44-48.	Thank you for your comment. For the prevalence review on complications of cystic fibrosis, one of the criteria for inclusion was sample size > 250 (please see appendix D for review protocols). The following study was already mentioned in the excluded studies list (appendix H): Blackwell 2005 (Exclusion reason: Sample size <251). The following studies have been assessed as ineligible for inclusion due to sample size <251,

				Orr, A., R. J. McVean, et al. (2001). "Questionnaire survey of urinary incontinence in women with cystic fibrosis." British Medical Journal 322(7301). Nixon, M., A. Glazner, et al. (2002). "Urinary incontinence in female adolescents with cystic fibrosis." Pediatrics 110(2). Daniels, Morrison, Lewis 2016 120 Moran, F., J. M. Bradley, et al. (2003). "Incontinence in adult females with cystic fibrosis: a Northern Ireland survey." International journal of clinical practice 57(3): 182-184 Blackwell, K., P. S. J. Malone, et al. (2005). "The prevalence of stress urinary incontinence in patients with cystic fibrosis: An under-recognized problem." Journal of pediatric urology 1(1): 5-9. Prasad, S. A., I. M. Balfour-Lynn, et al. (2006). "A comparison of the prevalence of urinary incontinence in girls with cystic fibrosis, asthma, and healthy controls." Pediatric pulmonology 41(11): 1065-1068. Vella, M., R. Cartwright, et al. (2009). "Prevalence of incontinence and incontinence-specific quality of life impairment in women with cystic fibrosis." Neurourology and urodynamics 28(8): 986-989 .Korzeniewska-Eksterowicz, A., I. Stelmach, et al. (2014). "Urinary incontinence in adolescent females with cystic fibrosis in Poland." Central European Journal of Medicine 9(6): 778-783. Nankivell, G., P. Caldwell, et al. (2010). "Urinary Incontinence in Adolescent Females with Cystic Fibrosis." Paediatric respiratory reviews 11(2): 95-99. Gumery L, Lee J, Whitehouse J et al. (2005) The prevalence of urinary incontinence in adult cystic fibrosis males [abstract] Journal of Cystic Fibrosis 4:S97 Burge, A. T., A. E. Holland, et al. (2011). "Prevalence and impact of incontinence in adult men with cystic fibrosis." Respirology 16.	however are not mentioned in the list of excluded studies list, because sample size was clear from the abstract and therefore we did not check the full text: Cornacchia 2001, Nixon 2002, Moran 2003, Vella 2009, Korzeniewska-Eksterowicz 2014. The following studies were checked full text based on your comment and were added to the excluded studies list (appendix H): Burge 2011; Orr 2001; Prasad 2006; White 2000 (All these 4 studies were excluded with exclusion reason: sample size <251); Nankivell 2010 (Exclusion reason: literature review); Gumery 2005 (Exclusion reason: Conference abstract. Sample size < 251). Notes have been added next to these studies' references in appendix H indicating that they were identified by stakeholders. Apologies but it was unclear what "Daniels, Morrison, Lewis 2016 120" refers to. Please note that the flow diagram of clinical article selection in appendix F has now been updated for this review to take into account these additional excluded studies.
British Thoracic Society	Full	290	17	The recommendation for use of NIV to support airway clearance techniques (ACT) does not appear to be supported by any published evidence. There is reference to a study (Young 2008) which evaluates the use of NIV for treatment of hypercapnia in which there is no reference to ACT as either a primary or secondary outcome measure.	Thank you for your comment. The study by Young (2008) met the protocol criteria because it compared NIV to no intervention (room air). We extracted data from this study on the outcomes outlined in the review protocol for airway clearance (appendix D). As per review protocol in appendix D, the evidence review did not assess for inclusion any studies that evaluated NIV as an adjunct to other airway clearance techniques. It only included studies that compared NIV (on its own) to no intervention or to another airway clearance technique. Given that the evidence on NIV used as an adjunct to other airway clearance techniques was not assessed for inclusion in the review, the recommendation to think about using non-invasive ventilation to help with airway clearance techniques has now been replaced with a recommendation to consider NIV in people with cystic fibrosis who have moderate or severe lung disease and cannot clear their lungs using standard airway clearance techniques. The full guideline explains the reasoning of the committee in relation to this point in more detail.
British Thoracic Society	Full	290	21	Regarding use of NIV to support ACT – it could be suggested that symptoms associated with reduced oxygen levels may be addressed with the application of controlled oxygen therapy to support ACT in the first instance with NIV therapy trial where indicated to address hypercapnia and hypoventilation.	Thank you for your comment. The recommendation to think about using non-invasive ventilation to help with airway clearance techniques has now been amended because, as per review protocol in appendix D, the evidence review did not assess for inclusion any studies that evaluated NIV as an adjunct to other airway clearance techniques. It only included studies that compared NIV (on its own) to no intervention or to another airway clearance technique. The recommendation has been amended to say consider NIV in people with cystic fibrosis who have moderate or severe lung disease and cannot clear their lungs using standard airway clearance techniques. The corresponding section in the full guideline has been amended to state that NIV unloads the respiratory muscles, therefore, it reduces the symptoms associated with respiratory muscle fatigue in moderate and severe lung disease such as reduced oxygen and breathlessness. The Committee also agreed that NIV can be beneficial as a short-term option in moderate disease, when people have difficulty clearing their airways using other clearance techniques, by unloading the respiratory muscles and reducing fatigue. The committee discussed your comment and noted that oxygen therapy alone while correcting oxygen levels will not unload the respiratory muscles and therefore allow better airway clearance and longer clearance sessions through the reduction of fatigue. The committee members noted that they would of course use oxygen for desaturation alone however, they would add NIV if patients were tiring or not achieving sufficient chest clearance with standard airway clearance techniques. The committee decided not to add this discussion on oxygen therapy to the full guideline because oxygen therapy was not included in the review protocol on airway clearance and was not included in the recommendations either.
British Thoracic Society	Short	10	Section 1.4.1	It doesn't mention respiratory failure, lung infection, acquisition of unusual and transmissible organisms	Thank you for your comment. The protocol of the review on the prevalence of complications of cystic fibrosis did not prioritise these complications. Therefore the evidence on the prevalence of these complications was not reviewed and no recommendations were made on this.
British Thoracic Society	Short	10	35	Should this mention GI cancers? Or even PTLD and solid organ malignancy	Thank you for your comment. The protocol of the review on the prevalence of complications of cystic fibrosis did not prioritise these complications, therefore the evidence on the prevalence of these complications was not reviewed and no recommendations were made on this. The

					committee discussed your comment and noted that PTLD is a complication of transplantation, not of cystic fibrosis. Moreover, the identification and management of GI cancers or other organ malignancies are not specific to cystic fibrosis.
British Thoracic Society	Short	11	18	Section 1.5.3 Frequency of review should be as clinically indicated and although mentioned elsewhere is should be emphasise that this review does not need to eb in the hospital. Bringing babies back every week in the first month of life is not appropriate. Some may not be diagnosed until 2 months of age anyway. Some less stable patients when older may need to be seen every couple of weeks. If guidance needs to be made then the statement should say the frequency of review depends on the stability of the patient and anticipated need to make treatment changes.	Thank you for your comment. The recommendation does not specify where the review should take place which allows options such as telemedicine to be considered. Based on their clinical experience and expertise, the committee agreed to recommend more frequent routine reviews after diagnosis and in early life. Following those initial years, the person's condition is likely to become more predictable. To guide the audiences reading the recommendation, the committee gave some examples of review frequency for different age groups, with frequency decreasing with age. The ranges of frequencies provided in the recommendation are not mandatory, only examples, and should be tailored to the individual with cystic fibrosis. A greater description of the committee's discussion on this area is provided in the full guideline section titled "evidence to recommendations".
British Thoracic Society	Short	11	25	Adult CF patients are not reviewed every 3-6 months, but flexibly according to need. Also this is contradicted in P12 line 1.	Thank you for your comment. The recommendation mentions an example of frequency of routine reviews for adults with cystic fibrosis every 3 to 6 months. As explained in the section "Evidence to recommendations", frequency of routine reviews would vary based on individual needs, therefore "3 to 6 months" is given as an example rather than as a standard to be followed for all adults. Given that the recommendation states "For example", it does not prevent more frequent or less frequent reviews and does not contradict any other routine review timetables in the guideline. The committee recommended routine reviews at least every 3 months for adults with clinical evidence of lung disease.
British Thoracic Society	Short	12	10-12	Cough swabs are not used in adult patients. This section is confusing as combines paediatric and adult management	Thank you for your comment. The committee discussed your comment and agreed that cough swabs can be used in adult patients. The section combines paediatric and adult management because most of the recommendations were the same in the two populations, therefore having two different sections would have led to a lot of repetition.
British Thoracic Society	Short	12	1	Adult patient are reviewed according to need. In sicker patients, pregnancy, pre transplant this is more frequently than 3 monthly. This statement contradicts p11 line 25	Thank you for your comment. The recommendation mentions an example of frequency of routine reviews for adults every 3 to 6 months. As explained in the section "Evidence to recommendations", frequency of routine reviews would vary based on individual needs, therefore "3 to 6 months" is given as an example rather than as a standard to be followed for all adults. Given that the recommendation states "for example", it does not prevent more frequent or less frequent reviews and does not contradict any other routine review timetables in the guideline. The committee recommended routine reviews at least every 3 months for adults with clinical evidence of lung disease.
British Thoracic Society	Short	12	1	It says pulmonary assessment every 3 months	Thank you for your comment. The committee recommended routine reviews at least every 3 months for adults with cystic fibrosis with clinical evidence of lung disease. A separate recommendation relating to the general population of adults with cystic fibrosis mentions an example of frequency of 3 to 6 months. As explained in the section "Evidence to recommendations", frequency of routine reviews would vary based on individual needs, therefore "3 to 6 months" is given as an example rather than as a standard to be followed for all adults. Given that the recommendation states "for example", it does not prevent more frequent or less frequent reviews and does not contradict any other routine review timetables in the guideline.
British Thoracic Society	Short	12	11	Some centres use cough plates instead of cough swabs or NPAs	Thank you for your comment. The committee discussed your comment and decided not to add cough plates to the recommendation because these are not widely used.
British Thoracic Society	Short	12	17	Currently no standardisation in the equipment used for LCI. So would need to have a comment about this and its use in measuring trends. LCI is a research tool, not generally available in CF centres.	Thank you for your comment. In the full guideline it is noted that LCI is currently in its infancy in the UK, but could provide additional respiratory information to spirometry. As a result the committee made recommendations to consider the use of LCI for those clinics that have access to the equipment and ability to interpret the results. To enable stronger recommendations in the future, a research recommendation to assess if LCI is a useful and cost-effective tool for the routine assessment and monitoring of changes in pulmonary status in people with cystic fibrosis was prioritised by the committee.
British Thoracic Society	Short	13	23	LCI - again feasibility	Thank you for your comment. In the full guideline it is noted that LCI is currently in its infancy in the UK, but could provide additional respiratory information to spirometry. As a result the committee made recommendations to consider the use of LCI for those clinics that have access to the equipment and ability to interpret the results. To enable stronger recommendations in the future, a research recommendation to assess if LCI is a useful and cost-effective tool for the routine assessment and monitoring of changes in pulmonary status in people with cystic fibrosis was prioritised by the committee.
British Thoracic Society	Short	13	24	In view of high radiation, the chest CT should only be done if the results are going to effect a change in treatment	The committee acknowledged that a CT scan costs considerably more than a chest X-ray and involves greater exposure to radiation. However, they believed a CT scan would show subtle structural changes in the lungs that would not be evident from a chest X-ray, such as early bronchiectasis. As a result, a CT scan could allow early escalation of treatment to prevent further deterioration that could be more costly to treat. Furthermore, the committee noted that the accuracy of CT scans to predict pulmonary exacerbations was demonstrated in the study by Sanders 2015. For these reasons, the committee concluded they could justify the use of CT scans as a cost-effective use of NHS resources and made a recommendation to think about

					doing a chest CT scan in people who have not had one before. The recommendation has now been amended to state a "low-dose" CT scan.
British Thoracic Society	Short	14	4-5	LCI - again feasibility	Thank you for your comment. In the full guideline it is noted that LCI is currently in its infancy in the UK, but could provide additional respiratory information to spirometry. As a result the committee made recommendations to consider the use of LCI for those clinics that have access to the equipment and ability to interpret the results. To enable stronger recommendations in the future, a research recommendation to assess if LCI is a useful and cost-effective tool for the routine assessment and monitoring of changes in pulmonary status in people with cystic fibrosis was prioritised by the committee.
British Thoracic Society	Short	14	6	Cough swabs not used in adults – again this is confusing as advice combined for Paediatric and adult patients	Thank you for your comment. The committee discussed your comment and agreed that cough swabs can be used in adult patients. The section combines paediatric and adult management because most of the recommendations were the same in the two populations, therefore having two different sections would have led to a lot of repetition.
British Thoracic Society	Short	15	6	HFCWO may have a role in those with reasons for not being able to do airway clearance by some other means (eg we have a young person with Cerebral palsy and CF, those who are less active)	Thank you for your comment. We have amended the recommendation to consider the use of high frequency chest wall oscillation in exceptional clinical circumstances as determined by the specialist CF team and following the NHS England policy on Individual Funding Requests. The section on evidence to recommendations in the full guideline explains that the CF team would use the NHS definition of exceptional clinical circumstances.
British Thoracic Society	Short	15	11	This is very vague comment. Currently rhDNAse is being offered to many children over 5-6 years per licence who have no reported symptoms but who demonstrate a benefit in terms of lung function and reduction in exacerbationss. .This statement can be interpreted	Thank you for your comment. The recommendation has been amended to refer to clinical evidence of lung disease rather than respiratory symptoms or other evidence of lung disease. As explained in the full guideline under "Consideration of clinical benefits and harms", the Committee discussed whether a mucoactive or mucolytic agent should be prescribed to everyone who has cystic fibrosis. However, taking into account the potential adverse effects, as well as the inconvenience and the cost of treatment, it was agreed not to recommend it to everyone; instead, the Committee agreed that it should be offered to people with cystic fibrosis who have clinical evidence of lung disease.
British Thoracic Society	Short	16	8	This goes against the CF Start study which has just been set up to answer this question. This statement should be taken out.or modified otherwise patients will not be able to be recruited to this important study	Thank you for your comment. The committee discussed your comment and concluded to keep the recommendation to offer flucloxacillin as antibiotic prophylaxis against respiratory *Staphylococcus aureus* infection for children with cystic fibrosis (although some amendments were made in relation to age cut-offs). The rationale for this recommendation is given in the full guideline. The committee noted that the evidence showed that anti-staphylococcal prophylaxis with an antimicrobial agent (either flucloxacillin or cephalexin) led to a decreased number of children in whom S aureus was isolated. Despite the fact that the evidence did not show this was associated with clinical benefit, there being no improvement in lung function or reduction in exacerbations in children given prophylaxis compared with those who were not, the reduction in *S aureus* was, nevertheless, a critically important outcome. Overall, the evidence did not reveal the occurrence of adverse events with prophylaxis. The committee were concerned about the theoretical possibility that long-term antimicrobial prophylaxis for *S aureus* might be associated with an increased risk infection with *P aeruginosa*. Although the evidence did not demonstrate this, the committee noted that the quality of the evidence for this outcome ranged from very low to low. The committee observed that, given the widespread expert consensus that this risk is a concern, they agreed that it could be mitigated by recommending that flucloxacillin be used rather than cephalexin. The fact that cephalosporins are broad spectrum is postulated to be the reason why an increase in pseudomonas isolation may be seen, although this is not known with certainty. Recommending flucloxacillin rather than a cephalosporin was in keeping with current practice. In contrast to current recommendations in the USA, the committee did not think there were grounds to advise the non-use of prophylaxis. This was based on the low cost of prophylaxis treatment and the potentially serious consequences of *S aureus* pulmonary infection that would outweigh the cost of prophylaxis.
British Thoracic Society	Short	16	7and 8 and 14	By convention it should be Staphylococcus aureus (Capital small_letter)	Thank you for your comment. We have ensured there is consistency when referring to Latin names of organisms to ensure they are compliant with NICE Style Guide. They are italicised and start with a capital letter. The genus names then abbreviated after first use in the full guideline but not in the short guideline where recommendations can be read as stand-alone recommendations so it was not felt appropriate to use abbreviations.
British Thoracic Society	Short	18	General	Pseudomonas aeruginosa? Note heading line 14 is correct and different from heading of Staphylococcus Aureus	Thank you for your comment. We have corrected the heading for *Staphylococcus aureus* to appear as *Staphylococcus aureus*.
British Thoracic Society	Short	19	23	We are unsure about evidence to support that.	Thank you for your comment. The discussion in the full guideline explains that no evidence was found for the treatment of *B cepacia* complex, therefore recommendations were based on committee's clinical expertise. The committee agreed that if a person develops a new infection with *B cepacia* complex, an attempt should be made to eradicate the infection with antibiotic therapy whether or not the person was unwell with the infection. The committee noted that it is important to treat new *B cepacia* complex infections effectively as chronic infection can cause a deterioration in lung function and, in some people, an overwhelming, and even fatal, infection called 'cepacia

					syndrome' may occur. Persistent isolation of *B cepacia* complex may also adversely impact on a persons' eligibility for transplantation. The committee noted that treating new infections with *B cepacia* complex is common practice in adult CF centres.
British Thoracic Society	Short	19	27	This cannot mean that in a patient with no pseudomonas or staphylococcus but with B cepacia you would NOT use nebulised tobramycin. Would you leave a cepacia patient on no long term antibiotics?	Thank you for your comment. The recommendation has now been amended to recommend to be aware that there is no evidence to support using antibiotics to suppress chronic *Burkholderia cepacia* complex infection in people with cystic fibrosis who have stable pulmonary status. The recommendation also states that the possible risks (for example, drug toxicity) of treating the infection should be discussed with the person and their family members or carers (as appropriate). The full guideline explains that no evidence was found for the treatment of *B cepacia* complex, therefore, recommendations were based on committee's clinical expertise. The committee advised that the long-term use of drugs used to suppress *B cepacia* complex can have adverse effects associated with additional treatment costs and quality of life decrements. Consequently, the committee did not want to recommend the use of those drugs in people who are chronically infected and stable, adding that reducing their treatment burden may subsequently promote adherence to their existing regimens and outweigh the benefits of suppressive treatment. However, the committee agreed that people who are deteriorating should consider a trial of chronic suppressive treatment with an inhaled antibiotic.
British Thoracic Society	Short	19	19 and 20	Burkholderia cepacia is correct I think you should change all to Capital small_letter eg Staphylococcus aureus	Thank you for your comment. We have ensured there is consistency when referring to Latin names of organisms to ensure they are compliant with NICE Style Guide. They are italicised and start with a capital letter. The genus names then abbreviated after first use in the full guideline but not in the short guideline where recommendations can be read as stand-alone recommendations so it was not felt appropriate to use abbreviations.
British Thoracic Society	Short	20	12-13	H influenza or h influenza?	Thank you for your comment. We have ensured there is consistency when referring to Latin names of organisms to ensure they are compliant with NICE Style Guide. They are italicised and start with a capital letter. The genus names then abbreviated after first use in the full guideline but not in the short guideline where recommendations can be read as stand-alone recommendations so it was not felt appropriate to use abbreviations.
British Thoracic Society	Short	20	13	Should this statement say do <u>not</u> treat if don't have evidence of a pulmonary infection?	Thank you for your comment. The committee discussed your suggestion and decided to keep the recommendation unchanged. The full guideline explains that no evidence was found for the treatment of *H influenzae*, therefore recommendations were based on committee's clinical expertise. The committee agreed it is important to treat *H influenzae* in order to prevent chronic infection with this pathogen. This is because although there might not be detectable evidence of disease due to it, the belief is that it will cause lung damage and so should be eradicated. They discussed 2 possible scenarios if a person develops an infection. If the person is clinically well (asymptomatic), the committee recommended giving an oral antibiotic agent. If the person is clinically unwell (for example, with cough or reduced lung function), they recommended the use of an oral or intravenous antibiotic treatment depending on the severity of the illness. These recommendations are consistent with clinical practice and with the CF Trust recommendations (CF Consensus document: antibiotic treatment for Cystic Fibrosis, 2009).
British Thoracic Society	Short	21	16	Is if "eradication "the correct term in NTM infection?	Thank you for your comment. The committee discussed your comment and noted that eradication would be the aim but not necessarily the result of non-tuberculous mycobacterial therapy. Therefore the recommendation has been amended to recommend to consider non-tuberculous mycobacterial therapy aimed at eradication.
British Thoracic Society	Short	21	22	[and Full] The NTM section needs clarification regarding which NTM as being discussed. – M abscessus (and for me recently M chelonae) are special cases as they are absolute contraindications to transplant whereas others M gordonae and as far as I know M avium are not. There is also the question of segregation of these from the CF ward and clinics. The full document suggests that MAC and Abscessus are being discussed together in the NTM section and only these organisms are being considered. These NTM organisms need to be discussed separately, under different sub - sections – particularly M abscessus.	Thank you for your comment. The recommendations do not specify which non-tuberculous mycobacteria (NTM) are being discussed because they apply to all NTM. These recommendations on NTM have been amended in order not to recommend which antibiotics should be considered or the duration of therapy aimed at eradication. Instead, the committee made a recommendation to seek specialist microbiological advice on this. The committee decided not to make more detailed recommendations, which would require us to differentiate between different NTM, because no evidence was found on NTM. However the full guideline mentions that the committee discussed the fact that the approaches to treating *M avium* complex and *M abscessus* differ (the full guideline mentions these two and no other NTMs because these two were the ones prioritised in the review protocol). The full guideline also mentions that there is existing consensus guidance on the management of non-tuberculous mycobacteria in a publication by Floto et al. (2016) titled "US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis" (http://thorax.bmj.com/content/71/Suppl_1/i1) With regards to segregation, the section of the guideline that focuses on preventing cross-infection includes multiple recommendations on cohorting and separating people individually. The committee did not make recommendations specific to non-tuberculous mycobacteria (NTM) in this section because no evidence was identified on NTM. However all recommendations in the cross-infection section except for those specific to *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex should apply to all people with cystic fibrosis, including those with NTM. This has now been explained in the full guideline.
British	Short	21	23	Good advice	Thank you for your comment.

Thoracic Society					
British Thoracic Society	Short	22	5	Is this referring to IgE or IgG?	Thank you for your comment. This recommendation has been modified to specify that elevated aspergillus serology refers to aspergillus-specific IgG and/or IgE.
British Thoracic Society	Short	22	19	Should monitor for NTM in those patients who are to start on long term azithromycin	Thank you for your comment. The committee agreed that no change to the recommendation was needed because NTM is measured at the annual assessment.
British Thoracic Society	Short	23	1	Free water intake and salt advice?	Thank you for your comment. The committee agreed that advice on water and salt intake did not need to be added to the recommendation because this is an implicit aspect of nutritional management. However this was added to the "Evidence to recommendations" section in the full guideline.
British Thoracic Society	Short	23	20	Children, young people and adults – why does document not refer to adults as well?	Thank you for your comment. We have amended the recommendation to state the test should be repeated if symptoms or signs suggesting malabsorption occur at any age.
British Thoracic Society	Short	24	19	Abdominal Xay should also be considered at least in children	Thank you for your comment. The recommendation states to consider further imaging for example with an abdominal ultrasound scan or abdominal CT scan for people who have an acute onset of peri-umbilical abdominal pain but no other clinical or radiological features of distal intestinal obstruction syndrome. Radiological features would be detected through an X-ray. This is now specified in the previous recommendation, which has been modified to state to suspect distal intestinal obstruction syndrome in people with cystic fibrosis who have an acute onset of peri-umbilical or right lower quadrant abdominal pain and any of the following: a palpable mass in the right lower quadrant; faecal loading in the right lower quadrant on a plain abdominal X-ray, especially if associated with small intestine air-fluid levels; clinical features of partial or complete intestinal obstruction, such as vomiting (especially bilious) and abdominal distension.
British Thoracic Society	Short	25	1	diatrizoate meglumine - use trade name as well Gastrograffin - not known by generic name – readers won't know what you are talking about.	Thank you for your comment. The NICE manual states that any references to products should be made in general terms to avoid giving the impression that NICE endorses a particular brand. However, in this case, the trade name has been used given that no other brands are available.
British Thoracic Society	Short	25	5	Poly ethylene glycol + Klean Prep – the trade names need to be added as well , otherwise no one will understand what to use	Thank you for your comment. The NICE manual states that any references to products should be made in general terms to avoid giving the impression that NICE endorses a particular brand. However "macrogols" have been added to the recommendation to increase the readers understanding.
British Thoracic Society	Short	25	7	What about colonoscopic washout with either Gastrorafin or N acetyl cysteine – we would do this before surgery and have never operated on anyone for DIOS.	Thank you for your comment. The committee agreed that consultation with a surgeon may identify colonoscopic washout as an option before surgery, however the committee decided not to include this in the recommendations because colonoscopic washout was not included in the review protocol and therefore evidence on this was not reviewed. This discussion has now been added to the section "Evidence to recommendations" in the full guideline.
British Thoracic Society	Short	25	7	Inta-Rectal treatment – colonic washouts not discussed - would consider prior to surgery prior to surgery	Thank you for your comment. The committee agreed that consultation with a surgeon may identify colonoscopic washout as an option before surgery, however the committee decided not to include this in the recommendations because colonoscopic washout was not included in the review protocol and therefore evidence on this was not reviewed. This discussion has now been added to the section "Evidence to recommendations" in the full guideline.
British Thoracic Society	Short	25	18	Need to be more precise about abnormal liver function tests	Thank you for your comment. The committee discussed your suggestion and decided not to include a definition of abnormal liver function blood tests to allow for clinical judgement to decide what tests are abnormal.
British Thoracic Society	Short	27	3	There are limited normative data for DXA scans for pre-pubertal children so difficult to interpret in children. Also no mention of the frequency	Thank you for your comment. The committee agreed that the recommendations on BMD should apply to children and adults, but noted that z-scores should be measured in children and t-scores in adults. In the full guideline section titled "evidence to recommendations" it states there is little value in routine monitoring, as children and young people get treated to help accrue bone mass in spite of the results of the test. The risk factors provided in the recommendation should be assessed during routine reviews to the clinic. In the full guideline section titled "evidence to recommendations" it is suggested that scans could be repeated on an annual basis if the BMD SDS score is less than -2.00. However, the committee did not state the frequency of bone scans in their recommendations as this would be individualised to the patient using clinical expertise.
British Thoracic Society	Short	29	4	No mention of NTM In terms of cross infection risks	Thank you for your comment. The recommendations specific to *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex were based on the clinical and economic evidence identified. The committee did not make recommendations specific to non-tuberculous mycobacteria (NTM) because no evidence was identified to make recommendations in addition to those that were not

					pathogen specific. All recommendations in this section except for those specific to *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex should apply to all people with cystic fibrosis, including those with NTM. This has now been explained in the full guideline.
British Thoracic Society	Short	29	5	pseudomonas aeruginosa but Burkholderia cepacia… in the same sentence ???	Thank you for your comment. The recommendation has been reworded for clarity and it now states to keep people with transmissible or chronic *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex infection separate from people who do not have these infections, for example by using separate outpatient clinics.
British Thoracic Society	Short	29	7	This is illogical 1. if they have the same genotype (VNTR/ PFGE) as it implies chronic infection even if you don't grow it and 2. If you have poor quality cough swabs vs sputum culture you lack sensitivity to say there is not chronic infection	Thank you for your comment. The recommendation has been amended to state intermittent isolation of *Pseudomonas aeruginosa*.
British Thoracic Society	Short	29	11	NOT using communal waiting areas – at present - this reads as though communal waiting areas are recommended, needs changing . Change to DO NOT use communal waiting areas?	Thank you for your comment. This bullet has been amended to "the use of communal areas" to remove the suggestion that waiting areas are used by some clinics. Communal areas was used in the recommendation to cover areas such as cafés, gyms and restrooms.
British Thoracic Society	Short	3	14	This statement is ambiguous. Should not make a diagnosis of CF with normal sweat test and normal gene results	Thank you for your comment. The committee agreed that a diagnosis based on clinical manifestations alone with normal test results could happen in some rare cases. The recommendation has now been modified to specify that this is rare.
British Thoracic Society	Short	30	4 and7	Ugh pulm exacerbation caused by ACUTE respiratory infection (viral or bacterial) Next section line 8 is meaningless – lungs of CF are chronically infected. Chronic pulmonary infection vs acute (pulmonary) exacerbation: respiratory and pulmonary should be considered interchangeable?	Thank you for your comment. We have amended the definitions for pulmonary exacerbation and infection to make it clearer.
British Thoracic Society	Short	32	27	chronic infection SHOULD be suppressed with long term antibiotics?	Thank you for your comment. The recommendations on antimicrobial treatments for each pathogen differ. Long-term antibiotic use was not considered to be effective for each pathogen under consideration.
British Thoracic Society	Short	4	11	Suggest nasal polyps included here	Thank you for your comment. The Committee decided not to include nasal polyps because they are very common in people without cystic fibrosis therefore they would not prompt an assessment for cystic fibrosis on their own. Moreover they are rare in children.
British Thoracic Society	Short	5	21-28	Mention cross infection here	Thank you for your comment. Managing the risks of cross-infection has been added to the recommendation.
British Thoracic Society	Short	5	21-28	Mention drugs alcohol smoking and sexually transmitted disease	Thank you for your comment. The committee considered your suggestion but concluded that advice on drugs, alcohol, smoking and sexually transmitted disease would not need to be tailored specifically for people with cystic fibrosis, instead the advice would be very similar to that given to the general population. As a result these topics have not been added to the recommendation.
British Thoracic Society	Short	5	1	'relevant information in clear English' might I suppose be better as 'using clear language which the patient/parents can understand'	Thank you for your comment. We have changed this from information in clear English to information that people with suspected or diagnosed cystic fibrosis and their family members or carers (as appropriate) can understand.
British Thoracic Society	Short	5	3	As CF affects non-English speakers should include some way of providing suitable information	Thank you for your comment. We have changed the wording of the recommendation from information in clear English to information that people with suspected or diagnosed cystic fibrosis and their family members or carers (as appropriate) can understand. The recommendations will not include translation issues because this is not specific to cystic fibrosis. The committee also included a recommendation which directs readers of this guideline to the NICE guideline CG138 "Patient experience in adult NHS services: improving the experience of care for people using adult NHS services". The CG138 guideline recommends: "Establish the most effective way of communicating with each patient and explore ways to improve communication. Examples include using pictures, symbols, large print, Braille, different languages, sign language or communications aids, or involving an interpreter, a patient advocate or family members".
British Thoracic Society	Short	5	29	After organ transplantation should have end of life care	Thank you for your comment. End of life care has been added to the recommendation.
British Thoracic Society	Short	8	21-24	The main issue in the guideline is the annual review process (sections 1.3.13 -Pharmacist and 1.3.14 -Psychologist): The guideline seems to imply that patients should see a pharmacist and psychologist for assessments at annual review, rather than having them available when needed. This may pose some difficulties for patients and CF teams. The annual review would now involve seeing 6 health care professionals (Doctor, Nurse, Physiotherapist, Dietitian, Psychologist, Pharmacist) which would be a very intense and prolonged process for patients. Many CF Centres currently make psychologist and pharmacists available when needed.	Thank you for your comment. The committee agreed that all the members of the multi-disciplinary team should assess the person with cystic fibrosis at the annual review, including the specialist clinical psychologist and the specialist pharmacist. This is consistent with the CF Trust Standards of Care 2011. The committee discussed your comment that the annual review could be a very intense and prolonged process. The committee noted that some centres do a rolling annual review (with different assessments performed at different times over the year), while other centres group all annual review assessments together. The committee did not make recommendations on this, thus leaving the choice to individual centres. Moreover, the recommendations (which have now been amended) specify that specialist pharmacists should advise people with cystic fibrosis on medicines optimisation not only at annual review but also at outpatient clinic visits, during inpatient admissions and on discharge from hospital. Specialist clinical psychologists should assess and advise people with cystic fibrosis and their family members or carers (as appropriate)

					at outpatient clinic visits and (if needed) at other outpatient appointments, during inpatient admissions, and at their annual review.
British Thoracic Society	Short	8	1	Diabetic nurse, working with CF Dietitian	Thank you for your comment. The committee agreed that the diabetic nurse would not always be part of the multidisciplinary team. The committee agreed that it was best to mention diabetes in a separate recommendation which states that the specialist cystic fibrosis multidisciplinary team should either include or have access to specialist expertise relevant to cystic fibrosis in the area of diabetes.
British Thoracic Society	Short	8	3	Access to play therapy (as well as clinical psychology)	Thank you for your comment. Play therapists support the delivery of care of a hospital or service and are not part of core service. They may be employed by the trust and would be accessed by all who need to have access to them. Overall, as play therapists are not utilised exclusively by people with cystic fibrosis they have not been added to the recommendation.
British Thoracic Society	Short	8	10	Again the Physiotherapy section of the MDT section seems more comprehensive than the other MDT members roles (not consistent).	Thank you for your comment. Some examples have been added to the recommendations about the social worker, specialist nurse, and specialist pharmacist, about their role on the MDT. The recommendation on the specialist dietitian and the specialist clinical psychologist do not include bullet points, but cross-refer to the section on nutrition and psychological assessment, respectively.
British Thoracic Society	Short	8	18	Dietitian should screen and monitor CF-related diabetes	Thank you for your comment. The committee discussed your suggestion but decided not to include it because the whole multidisciplinary team is responsible for monitoring indicators of CF-related diabetes.
British Thoracic Society	Short	8	18	It is inconsistent to have bullet points for physiotherapy and not for any other discipline for advice – either collapse section 1.3.12 or expand each other section . Physiotherapy section seems larger than other sections – inconsistent.	Thank you for your comment. Some examples have been added to the recommendations about the social worker, specialist nurse, and specialist pharmacist about their role on the MDT. The recommendation on the specialist dietitian and the specialist clinical psychologist do not include bullet points, but cross-refer to the section on nutrition and psychological assessment, respectively.
British Thoracic Society	Short	9	11	Renal? For aminoglycoside toxicity, antibiotic nephritis and post transplant	Thank you for your comment. The committee discussed your suggestion but decided not to include nephrology because management in this area would not differ between people with cystic fibrosis and the general population.
British Thoracic Society	Short	9	12	Mention ENT here under specialist expertise	Thank you for your comment. ENT surgery has been added to the list.
British Thoracic Society	Short	General		Please use standard nomenclature for organisms throughout the document, currently not consistent. There is a mixture of “staphylococcus aureus” and “Staphlococcus aureus” (correct), and for other organisms too. The document would be improved by consistency in this area.	Thank you for your comment. We have ensured there is consistency when referring to Latin names of organisms to ensure they are compliant with NICE Style Guide. They are italicised and start with a capital letter. The genus names then abbreviated after first use in the full guideline but not in the short guideline where recommendations can be read as stand-alone recommendations so it was not felt appropriate to use abbreviations.
British Thoracic Society	Short	General		In sections 1.5 Annual and routine review, 1.6 Pulmonary monitoring and assessment – the document combines paediatric and adult management in each section. This approach is confusing, and leads to a lack of clarity in these sections.	Thank you for your comment. The committee considered your suggestion but agreed not to separate the reviews by adults and children as there is a lot of overlap. Where reviews are specific to adults and children we have stated that.
British Thoracic Society	Short	General		No mention of small molecule treatments	Thank you for your comment. Small molecule treatments were not included in the scope as current clinical practice in that area was considered to be consistent and effective, relative to the other areas under consideration. For completeness, a recommendation referring to the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation has been added.
British Thoracic Society	Short	General	General	Pregnancy should be mentioned even in the short guideline. We are surprised there is no mention of ensuring genotype is determined given the development of new specific CFTR enhancing drugs. Likewise no mention of transplantation.	Thank you for your comment. The referral for, and management of, transplantation and management of cystic-fibrosis-related fertility and pregnancy problems were areas included in the scope, as areas that would not be covered by the guideline as current clinical practice in those areas was considered to be consistent and effective relative to other areas under consideration. Instead, evidence was sought to produce recommendations in areas with greater clinical uncertainty.
British Thoracic Society	Short	General	General	We are also surprised that there is no mention of transplantation.	Thank you for your comment. The referral for, and management of, transplantation was an area included in the scope as an area that would not be covered by the guideline as current clinical practice in this area was considered to be consistent and effective relative to the other areas under consideration. Instead, evidence was sought to produce recommendations in areas with greater clinical uncertainty.
Chiesi Limited	Appendix D	46		We are concerned that nebulised tobramycin was excluded from the search for treatments for the management of chronic *Pseudomonas aeruginosa* infection, and that only dry powder tobramycin was included. We suggest that the search be re-run, including terms to identify papers examining nebulised tobramycin in this clinical situation (see comment 4).	Thank you for your comment. The search strategy for this review (Appendix E) was not limited to the preparation of tobramycin. Papers that assessed tobramycin dry powder and nebulised tobramycin were included in this review. The protocol in Appendix D has been amended to include nebulised tobramycin as the omission was an error.
Chiesi Limited	Full	294	33	We suggest that data on mannitol in children and young people should have been included for consideration in this review. On that basis, we would like to suggest the inclusion of evidence from the study reported by Teper et al, 2011,[1] be included in the evidence review. The study is not of shorter duration or	Thank you for your comment. Mannitol in children and young people was an intervention in the protocol, therefore evidence on children and young people was included. Data on Aitken 2012 and Bilton 2011 had been included for all age groups but had not been stratified by age. This stratified analysis has now been included in the review. The study by Teper et al. was excluded in the evidence review with this reason: Dose-response study. This comparison has not been

				smaller patient numbers than other studies included in the review. We would also like to draw the committee's attention to a recently-published paper, the CF-204 study, a randomised, placebo-controlled crossover study comparing 8 weeks of treatment with inhaled mannitol with placebo in children aged 6-17 years.[2] The authors report, with mannitol, an improvement of 3.42% in percent predicted FEV1 and a reduction in pulmonary exacerbations; a similar incidence of adverse events was observed between groups. 1. Teper A., Jaques A., Charlton B., Inhaled mannitol in patients with cystic fibrosis: A randomised open-label dose response trial, Journal of Cystic Fibrosis, 10, 1-8, 2011 2. De Boeck K., Haarman E., Hull J., Lands L.C., Moeller A., Munck A., Riethmuller J., Tiddens H., Volpi S., Leadbetter J., Charlton B., Malfroot A., for the DPM-CF-204 Study Group, Inhaled dry powder mannitol in children with cystic fibrosis: A randomised efficacy and safety trial, Journal of Cystic Fibrosis, 16, 380-387, 2017	prioritized for inclusion in the review. (Please see list of excluded studies in appendix H). The study by De Boeck was published in May 2017. The cut-off date for the search on mucoactive agents was 5 January 2017. Therefore this study was not assessed for inclusion. Relevant studies published after the cut-off search date will be included in future updates of this guideline. The committee noted that mannitol is rarely used in clinical practice in children and young people. They were aware of issues of poor tolerability and difficulties with the inhaler device in children and young people. The committee agreed that mannitol may be an option for children and young people when rhDNase and hypertonic sodium chloride have failed or are not tolerated and so has now made a recommendation to this effect.
Chiesi Limited	Full	322	24-36	We disagree with the conclusion given that evidence of low-moderate quality finds no clinically significant difference in lung function measured by FEV1 produced by inhaled mannitol. The conclusions drawn by the authors in the publications of the cited clinical trials was that the mean difference in lung function between inhaled mannitol, and a comparator of low-dose mannitol as placebo, was clinically meaningful. Bilton et al, 2011, found, over 26 weeks, an improvement from baseline of 6.5% for mannitol-treated patients vs 2.4% for placebo-treated patients.[1] In a very similar trial, Aitken et al, 2012, found an improvement of 8.22% for mannitol-treated patients and 4.47% for placebo-treated patients.[2] Secondary endpoints in both trials, including change in percent predicted FEV1 (3.60% and 2.42%, compared to placebo), corroborate the finding.[1,2] 1. Bilton, D., Robinson, P., Cooper, P., Gallagher, C. G., Kolbe, J., Fox, H., Jaques, A., Charlton, B., C. F. Study Investigators, Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study, European Respiratory Journal, 38, 1071-80, 2011 2. Aitken, M. L., Bellon, G., De Boeck, K., Flume, P. A., Fox, H. G., Geller, D. E., Haarman, E. 12 G., Hebestreit, H. U., Lapey, A., Schou, I. M., Zuckerman, J. B., Charlton, B., C. F. Investigators, Long-term inhaled dry powder mannitol in cystic fibrosis: an international randomized study, American Journal of Respiratory & Critical Care Medicine, 185, 645-52, 2012	Thank you for your comment. The mean difference in the lung function (measured as change in FEV1 % predicted) between the intervention and control groups was less than 5%, which was the minimal important difference for this outcome, as specified in the review protocol (appendix D). Therefore, the evidence statements for the mixed population of children, young people and adults state that the evidence showed no clinically significant difference between the intervention and control groups. Additional evidence statements have now been included based on a stratified analysis by age.
Chiesi Limited	Full	387	27	We are concerned that evidence for only dry powder tobramycin, not nebulised tobramycin, was considered for the treatment of chronic *Pseudomonas aeruginosa* infection (see comments 1, 6). Nebulised tobramycin (as Bramitob ®) is licensed for the treatment of chronic *Pseudomonas aeruginosa* infection and is included in the recommendations. If the search protocol had included terms for chronic treatment, an additional paper would have been identified: Mazurek H et al, Pediatr Pulmonol 2014, 49:1076-1089. Long term-efficacy and safety of aerosolized tobramycin 300mg/4mL in cystic fibrosis. We suggest that the scope of the recommendations be reviewed to include an examination of the data on nebulised tobramycin in the management of chronic *Pseudomonas aeruginosa.*	Thank you for your comment. The omission of nebulised tobramycin in the protocol was due to an oversight therefore the protocol has now been amended (Appendix D). The search strategy for this review (Appendix E) was not limited to the preparation of tobramycin. The evidence review also includes the following studies where nebulised tobramycin is at least one of the interventions: NICE TA 276; Chuchalin 2007; Hodson 2002; Konstan 2011a; Lenoir 2007; Murphy 2004; Ramsey 1993; Ramsey 1999; Flume 2016. Mazurek et al. 2014 compared two preparations of nebulised tobramycin (TOBI and Bramitob) but comparisons of preparations were not included in the protocol.
Chiesi Limited	Full	450	3	We are concerned that nebulised tobramycin has been considered as a single treatment, whereas two distinct preparations are available, 300mg/5mL (TOBI ®), and 300mg/4mL (Bramitob ®) with distinct safety and tolerability profiles. We suggest that the two preparations be considered separately, both from a clinical and a health economic perspective.	Thank you for your comment. The Committee agreed it was reasonable to assume equivalent efficacy across those preparations and comparisons of preparations were not included in the protocol (appendix D). In the economic model, the cheapest preparation is considered in the base case to reflect the best price available to the NHS. However, there is an option in the model to apply the more expensive preparation. Moreover, given that NICE cannot be seen to endorse a particular brand the generic name is used.
Chiesi Limited	Full	458	16-18	We are concerned that nebulised tobramycin has been included as a treatment for people are who clinically deteriorating due to chronic *Pseudomonas aeruginosa* despite regular inhaled colistimethate sodium, without the consideration of the evidence given by Mazurek at al, 2014, which was excluded from the search results due to the protocol not seeking evidence for nebulised tobramycin in chronic *Pseudomonas aeruginosa* infection.	Thank you for your comment. The omission of nebulised tobramycin in the protocol was due to an oversight therefore the protocol has now been amended. The search strategy for this review (Appendix E) was not limited to a specific preparation of tobramycin and also included nebulised tobramycin. The evidence review also includes the following studies where nebulised tobramycin is at least one of the interventions: NICE TA 276; Chuchalin 2007; Hodson 2002; Konstan 2011a; Lenoir 2007; Murphy 2004; Ramsey 1993; Ramsey 1999; Flume 2016. Mazurek et al. 2014 compared two preparations of nebulised tobramycin (TOBI and Bramitob) but this comparison was not included in the protocol.
Chiesi Limited	Full	458	7-9	We suggest that the committee consider the use of nebulised tobramycin for patients not suitable for nebulised colistimethate sodium, when there is evidence of ongoing *Pseudomonas aeruginosa* infection without a requirement for continued clinical deterioration, i.e. alongside colistimethate sodium DPI (see also comment 1).	Thank you for your comment. The guideline must adopt existing TA recommendations. Recommendation 1.6.34 taken from TA 276 states nebulised colistimethate is the first line treatment and recommends colistimethate sodium dry powder inhalation as the second line treatment. Recommendation 1.6.37 also taken from TA 276 states people should consider stopping treatment if there is no clinical benefit.
Chiesi Limited	Full	General	Section	In the management of chronic *Pseudomonas aeruginosa*, an example of good practice may be to use a test pack of tobramycin for the initial patient test so as to minimise the potential for batch	Thank you for your comment. We agree that waste should be minimised. However, the committee agreed that the reduction of pharmacy waste is not specific to cystic fibrosis and should be

			9.4	vial waste and to adhere to the pharmacy waste reduction best compilation paper.[1] Without this test pack health care professionals would need to open a month's treatment to test one patient. 1. Pharmaceutical waste reduction in the NHS: A best practice compilation paper. June 2015. Accessed at: https://www.england.nhs.uk/wp-content/uploads/2015/06/pharmaceutical-waste-reduction.pdf (we can remove this link)	considered as standard practice across all disease areas. Instead of adding a recommendation, a short narrative regarding pharmacy waste reduction has been added to the full guideline.
Chiesi Limited	Short	18	23-26	We suggest aligning the recommendation for the use of nebulised tobramycin with the NICE TA 276 recommendation for DPI tobramycin. We suggest replacing the current text : For people who are clinically deteriorating despite regular inhaled colistimethate sodium, consider nebulised aztreonam, nebulised tobramycin, or tobramycin DPI (see recommendation 1.6.36 on using tobramycin DPI). With: For people where colistimethate sodium is contraindicated, not tolerated, has not produced an adequate clinical response, or who are clinically deteriorating consider nebulised aztreonam, nebulised tobramycin, or tobramycin DPI (see recommendation 1.6.36 on using tobramycin DPI).	Thank you for your comment. We agree with your suggestion however the TA did not define tolerance or adequate clinical response. For this reason we could not add these criteria to our recommendation with confidence.
Cystic Fibrosis Trust	Appendices	General	General	For some aspects of cystic fibrosis management, NICE has already produced guidance. These pieces of guidance need to be included in the body of the full NICE guidelines to ensure that stakeholders can easily reference guidance on available care for people with cystic fibrosis.	Thank you for your comment. The pathway that will be developed for the guideline will cross refer to relevant NICE documents such as Technology Appraisals and Clinical Guidelines. There is also a section in the full guideline titled "Related NICE guidance" which may highlight the guidance you are referring to.
Cystic Fibrosis Trust	Full	127	General	The guideline highlights the importance of information and support but does not identify reliable and responsible sources. The Cystic Fibrosis Trust publishes comprehensive information resources for people with cystic fibrosis and their families and carers complied with independent input from cystic fibrosis specialists and people with cystic fibrosis. In 2016-2017 we published information resources about starting primary and secondary school, end of life care and advanced care planning. Our resources for people with CF and their partners who are considering starting a family, has been downloaded over 1500 times, showing the need for information in this area. Another area where people with cystic fibrosis of all ages can struggle to find trustworthy support is online. The Cystic Fibrosis Trust social media channels are moderated to provide support in a safer environment. Our helpline services are also available both by telephone and email. Our helpline took 3,721 enquiries in 2016. We would welcome inclusion here as a trusted source of information for people to be directed to.	Thank you for your comment. The committee discussed your suggestion and decided not to go into detail on reliable sources of information in the recommendations, however the section "Evidence to recommendations" mentions that the committee agreed it is important to advise people with cystic fibrosis and their parents to be aware of the potential issues when they use the internet to look up for health information. However, information and support available from trustworthy sources of information, such as the NHS, CF Trust (and its international counterparts) could be signposted to. They also agreed it is important to give the person with cystic fibrosis and the families an opportunity to discuss what they have read.
Cystic Fibrosis Trust	Full	285-292	6-7	We do not believe the recommendation 'do not offer high-frequency chest wall oscillation as an airway clearance technique for people with cystic fibrosis' should be included in the guideline. Whilst current evidence does not show high-frequency chest wall oscillation to be superior to manual physiotherapy, PEP mask, ACBT and AD no evidence for patient preference was found for this critical outcome (p.285). Physical airway clearance therapy is time consuming, intrusive, requires a high level of expertise and is often uncomfortable for people with cystic fibrosis. As reported in the guidance increasing numbers of patients have paid for high-frequency chest wall oscillation privately, displaying strong patient preference. As identified by the Cochrane Review in March 2017 (http://www.cochrane.org/CD006842/CF_use-vibrating-devices-help-people-cystic-fibrosis-clear-their-airways-mucus) 'more adequately-powered long-term randomised controlled trials are necessary and outcomes measured should include frequency of exacerbations, individual preference, adherence to therapy and general satisfaction with treatment. Increased adherence to therapy may then lead to improvements in other parameters, such as exercise tolerance and respiratory function.	Thank you for your comment. Moderate quality evidence from 2 trials showed that PEP was better at reducing pulmonary exacerbations than HFCWO. Based on this, the committee agreed that HFCWO should not be recommended as part of this guideline. However, the recommendation has been amended to consider the use of HFCWO in exceptional clinical circumstances as determined by the specialist CF team and following the NHS England policy in individual funding requests. The full guideline explains that the CF team would use the NHS definition of exceptional clinical circumstances.
Cystic Fibrosis Trust	Full	667	32	Reference to "in times of austerity" could be construed as politically-motivated and should be removed.	Thank for your comment. This sentence has been amended to address your comment.
Cystic Fibrosis Trust	Full (*Short*)	14 (*32*)	13-15 (*21-23*)	The guideline states 'A FEV1 of 50% and above will enable people live relatively normal lives and is associated with fewer difficulties in completing activities of daily living.' This is not supported by a source and provides an unhelpful oversimplification of the nature of the condition, which is recognised elsewhere in the document as a multi-system disorder. Gastro-intestinal issues, CF-related diabetes and high treatment burden are three examples (of many) that are common challenges for people with CF (regardless of lung function) and barriers to living 'relatively normal lives'. Whatever the motivation for the inclusion of this statement, we strongly suggest it is removed.	Thank you for your comment. The statement which included FEV1 values has been amended to state "FEV1 is a key predictor of life expectancy in people with cystic fibrosis, and optimising lung function is a major goal of care."
Cystic Fibrosis Trust	Full/Short	General	General	The Cystic Fibrosis Trust support national evidence-based recommendations on cystic fibrosis practice and welcome the NICE Guideline 'Cystic fibrosis: diagnosis and management.' The NICE	Thank you for your comment.

				Guideline recognises the complexity of cystic fibrosis care and the importance of holistic, multi-disciplinary support for people with cystic fibrosis, and high-quality dialogue and involvement of people with CF and their families in decisions made about their care.	
Cystic Fibrosis Trust	Full/Short	General	General	The UK CF Registry is inconsistently referred to as 'the UK registry' (p.14), the 'CF UK registry' (p.32), 'CF registry' (p.32), 'the Cystic Fibrosis Registry' (p.175), UK CF Trust registry (p.212, 219).	Thank you for your comment. We have amended all references to the UK CF registry to "UK CF Registry".
Cystic Fibrosis Trust	Full/Short	General	General	The UK CF Registry is highlighted in the Guidance as a priority source. Over 99% of people with cystic fibrosis consent to their anonymised data being collected in the UK CF Registry, which utilises data for research, annual reporting, quality improvement, and as the evidence base for the cost of cystic fibrosis care, informing proportionate year-of-care tariff payments by NHS England. It is also relied upon by the European Medicines Agency to evaluate the safety and efficacy of therapies for post-marketing surveillance. The Guideline shows that the UK CF Registry contains evidence which is not found anywhere else and is vital to understanding and managing cystic fibrosis, to work towards ensuring everyone with cystic fibrosis can look forward to a long and healthy life. Recognising the importance of maintaining, developing and investing in the UK CF Registry as a common asset for the purposes stated above is critical, both at an operational (e.g. data entry) and strategic level (e.g. UK CF Registry Steering Committee).	Thank you for your comment.
Cystic Fibrosis Trust	Full/Short	General	General	We welcome the research priorities set out in the guideline, which – in part – complement the research priorities which the Cystic Fibrosis Trust has identified in collaboration with the James Lind Alliance (JLA) Priority Setting Partnership (PSP) for cystic fibrosis. The James Lind Alliance Priority Setting Partnership in cystic fibrosis brought together over 500 people from across the world and includes an even split of medical staff and lay people. This is the first time such a collaborative and representative process has been undertaken in cystic fibrosis. The work continues with the National Institute for Health Research (NIHR), the Cystic Fibrosis Trust, the Cystic Fibrosis Foundation and the UK Research Councils supporting the research questions identified to be funded and taken forward by experienced and collaborative researchers.	Thank you for your comment and your support.
Cystic Fibrosis Trust	Full/Short	General	General	It is unclear why CFTR-modulating therapies are not referenced in these guidelines, other than in relation to adherence and related impacts on cost-effectiveness (p.665-667). The Cystic Fibrosis Trust requests an explanation for this decision. Furthermore, the Committee's suggestion to ration disease-modifying therapies (p.667) has no place in NICE Guidelines and the line "…such contracts should only be offered to people with cystic fibrosis who are treatment compliant to ensure the benefits from treatment can outweigh the high cost of treatment" must be removed. Definitions of 'treatment compliance' are not offered and the ethical implications are not considered.	Thank you for your comment. CFTR modulators were not included in the scope as current clinical practice in this area was considered to be consistent and effective, relative to the other areas under consideration. For completeness, a recommendation referring to the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation has been added. When the Committee made their recommendations, the Equality and Impact Assessment (EIA) form was referred to, to ensure equality issues were considered. Equality issued are documented in the full guideline in the sections titled "other considerations". The sentence on disease-modifying therapies has been removed as suggested. The Committee did not think it was appropriate to define treatment compliance as the range would be individualised to the patient and the intervention.
Cystic Fibrosis Trust	Short	8	4	Regarding the support of social workers within the CF MDT, the use of the word 'specialist' is conspicuous by its absence. Whilst the Cystic Fibrosis Trust recognises that specialism within this discipline is harder to define than for clinical roles, we suggest that this adjective is included regarding social workers, as expertise in the impact of cystic fibrosis on an individual's life can profoundly improve the outcomes delivered by social worker intervention. This is particularly important in relation to the positive impact that high-quality social worker support can have on the ability of clinical colleagues within the MDT to focus on their primary duties. Inexperience with cystic fibrosis or a lack of continuity in personnel support may impact negatively on delivery of primary clinical duties. Additionally, high-quality support may enable individuals to better engage with their clinical team and self-manage care at home – a critical element of cystic fibrosis care.	Thank you for your comment. It was not within the scope of this guideline to specify the specialism of cystic fibrosis social workers as this guideline only applies to NHS settings and social workers, while working within NHS settings, are not employed by the NHS. The recommendations have been amended to state that the specialist cystic fibrosis multidisciplinary team should either include, or have access to, social workers.
Cystic Fibrosis Trust	Short	9	27-28	The guidance states: "The specialist cystic fibrosis centre should take responsibility for ensuring transitions are successful." It is unclear which service (paediatric or adult) should assume this responsibility. This should be clarified.	Thank you for your comment. ~~The recommendation has been amended to refer to paediatric and adult centres~~. This recommendation has been deleted from the guideline and readers are instead directed to NICE guideline NG43 "Transition from children's to adults' services for young people using health or social care services"
Department of Health	General	General		Thank you for the opportunity to comment on the draft for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.

MAP BioPharma Limited	Full	19	18-28	Related to comment 1, since the draft guideline fails to make any mention of CFTR modulators, as a minimum, it should be explicitly stated in section 3.5 that these are not within the remit of the guidelines. However, it would be preferable to include recommendations on the use of CFTR modulators within the guideline.	Thank you for your comment. CFTR modulators were not included in the scope as current clinical practice in this area was considered to be consistent and effective, relative to the other areas under consideration. We cannot add CFTR modulators as an exclusion from the scope in section 3.5 at this stage as the scope is defined and finalised prior to guideline development. For completeness, a recommendation referring to the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation has been added.
MAP BioPharma Limited	General	General	General	We are concerned at the precedent that might be set if NICE Clinical Guidelines do not routinely take into consideration recommendations in NHS England clinical commissioning policies. This concern comes from the omission of CFTR modulators from the draft guideline. There is no reference made anywhere in the documentation relating to the availability of CFTR modulators and their importance in the management of CF patients, or alternatively, any clarification that these were outside the remit of the guideline. Two products are currently licensed for treating cystic fibrosis in various indications (ivacaftor and lumacaftor plus ivacaftor in combination). Ivacaftor (in cystic fibrosis patients aged 2 or older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R) is routinely commissioned by NHS England and is recommended by the All Wales Medicines Strategy Group (AWMSG). It therefore seems remarkable that no reference is made to CFTR modulators in this clinical guideline, which has a remit of guiding best practice in the diagnosis and management of cystic fibrosis. This has the potential to cause misunderstandings and confusion regarding the reimbursement status of these products and their use in current clinical practice. We would suggest that recommendations regarding the use of CFTR modulators are therefore made based on the relevant clinical commissioning policies that are in place.	Thank you for your comment. CFTR modulators were not included in the scope as current clinical practice in this area was considered to be consistent and effective, relative to the other areas under consideration. For completeness, a recommendation referring to the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation has been added.
Neonatal and Paediatric Pharmacists Group (NPPG)	Short	11	15	We welcome the recommendation that the annual review should include an assessment by a pharmacist.	Thank you for your comment.
Neonatal and Paediatric Pharmacists Group (NPPG)	Short	15	18-26	Mannitol use in children has not been reviewed. A phase 2, randomised, placebo-controlled crossover study has been published recently. This showed that inhaled mannitol was associated with significant improvements in lung function and sputum weight, irrespective of rhDNase (recombinant human deoxyribonuclease) use, age or disease severity. Inhaled mannitol was well tolerated and was associated with a reduced incidence of pulmonary exacerbation adverse events. De Boeck K, Haarman E, Hull J *et al*. Inhaled dry powder mannitol in children with cystic fibrosis: A randomised efficacy and safety trial. J Cyst Fibros. 2017 May;16(3):380-387. doi: 10.1016/j.jcf.2017.02.003. Epub 2017 Mar 1. We would suggest that this evidence is also reviewed so that recommendations can be made regarding the use of mannitol in children as a mucoactive agent.	Thank you for your comment. Mannitol in children and young people was an intervention in the protocol, therefore evidence on children and young people was included. Data on Aitken 2012 and Bilton 2011 had been included for all age groups but had not been stratified by age. This stratified analysis has now been included in the review. The study by Teper et al. was excluded in the evidence review with this reason: Dose-response study. This comparison has not been prioritized for inclusion in the review. (Please see list of excluded studies in appendix H). The study by De Boeck was published in May 2017. The cut-off date for the search on mucoactive agents was 5 January 2017. Therefore this study was not assessed for inclusion. Relevant studies published after the cut-off search date will be included in future updates of this guideline. The committee noted that mannitol is rarely used in clinical practice in children and young people. They were aware of issues of poor tolerability and difficulties with the inhaler device in children and young people. The committee agreed that mannitol may be an option for children and young people when rhDNase and hypertonic sodium chloride have failed or are not tolerated and so has now made a recommendation to this effect.
Neonatal and Paediatric Pharmacists Group (NPPG)	Short	33	16-27	We welcome the recommendation that more research is needed on whether all children with meconium ileus should receive ursodeoxycholic acid to reduce the risk of liver disease.	Thank you for your comment.
Neonatal and Paediatric Pharmacists Group (NPPG)	Short	7-8	2	We welcome the recommendation that a specialist pharmacist should be included in the multidisciplinary team.	Thank you for your comment.
NHS England	General	General		•The guidelines appear comprehensive and set out key outlines for services. •The shortened guidelines appear entirely appropriate and follow best evidence based practice. •The guidelines are helpful are will provide a strong case for ensuring good quality care and are largely in keeping with clinical UK practice. •The recommendations are not particularly contentious. The nature of the document which is also to be read by lay people means that much of it makes statements that are unlikely to change existing practice. There are also a number of 'think about' or 'consider' in the recommendations.	Thank you for your comment.
NHS England	General	General		The abbreviation DIOS usually stands for distal intestinal obstruction syndrome rather than ileal and this should be amended throughout section 1.7.8 and 1.7.16 (NICE guideline).	Thank you for your comment. The recommendations have now been amended to use the term distal intestinal obstruction syndrome.
NHS England	General	General		It would be helpful to include information in a range of languages or access to translation (page 5 line 3).	Thank you for your comment. We have changed the wording of the recommendation from information in clear English to information that people with suspected or diagnosed cystic fibrosis and their family members or carers (as appropriate) can understand. The recommendations will not include translation issues because this is not specific to cystic fibrosis. The committee also

					included a recommendation which directs readers of this guideline to the NICE guideline CG138 "Patient experience in adult NHS services: improving the experience of care for people using adult NHS services". The CG138 guideline recommends: "Establish the most effective way of communicating with each patient and explore ways to improve communication. Examples include using pictures, symbols, large print, Braille, different languages, sign language or communications aids, or involving an interpreter, a patient advocate or family members".
NHS England	General	General		It would be prudent to specify what level of contact (day and night) is the minimum, as this is currently left to interpretation (page 7, line 17)	Thank you for your comment. The committee agreed that the recommendation did not need to be more specific about the level of contact people can expect as a minimum because each centre will have their own process for providing this. There should be existing clear processes in place for accessing out of hours at each clinic.
NHS England	General	General		MDT specifics – W.T.E guidance would be beneficial as could be as little as for example, half a day specialist nurse cover, if part of a wider role (page 7, line 28).	Thank you for your comment. WTEs are provided in appendix K for a range of clinic sizes. However, the Committee did not want to include WTEs in their recommendations to prevent interpretation of a minimum. Instead, the Committee agreed WTEs should depend on the complexity of people with cystic fibrosis at each clinic. The Committee's discussion on this area is provided in the full guideline section titled "evidence to recommendations"
NHS England	General	General		Are there any alternatives if allergic to penicillin (page 16, line 8)?	Thank you for your comment. We have amended the recommendation to state that if children are allergic to penicillins, an alternative oral anti- staphylococcus aureus agent should be considered.
NHS England	Short		1.1.1	It would be worth making reference to the National Guideline on sweat testing as it is important that only units who do sufficient number of sweat tests (generally thought to be 50 a year) should be carrying out this test. Otherwise, it should be done in a CF Specialist Centre.	Thank you for your comment. The committee did not make reference to this sweat test guideline in the recommendation because NICE recommendations can only endorse guidelines that follow NICE processes and have been approved by NICE. However, in the section "Evidence to recommendations" in the full guideline, a reference has been added to the Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK, 2nd Version, by RCPH.
NHS England	Short		1.2.3	- It says that relevant information should be given in clear English. It makes no mention of those in whom English is not their first language and there are a proportion of CF patients from Europe and Asian for whom English is not the first language. Mention should therefore be made of appropriate translations.	Thank you for your comment. We have changed the wording of the recommendation from information in clear English to information that people with suspected or diagnosed cystic fibrosis and their family members or carers (as appropriate) can understand. The recommendations will not include translation issues because this is not specific to cystic fibrosis. The committee also included a recommendation which directs readers of this guideline to the NICE guideline CG138 "Patient experience in adult NHS services: improving the experience of care for people using adult NHS services". The CG138 guideline recommends: "Establish the most effective way of communicating with each patient and explore ways to improve communication. Examples include using pictures, symbols, large print, Braille, different languages, sign language or communications aids, or involving an interpreter, a patient advocate or family members".
NHS England	Short		1.3.15	- Ear, nose and throat surgeon should be included in this list to help with the common problem of nasal polyps and recurrent sinusitis.	Thank you for your comment. ENT surgeons were included in the protocol as an extended member of the MDT and their importance is discussed in the full guideline. ENT surgeons have been added to the recommendation as suggested.
NHS England	Short		1.4.1 and 1.4.2	- Section 1.4.1 states that a common complication of arthralgia (1.4.1) and Section 1.4.2 states the less common complication of CF related arthritis. This is not clear and one normally uses the term CF-related arthropathy to cover all forms of joint pains.	Thank you for your comment. The committee discussed your comment and agreed not to change the recommendations on this because arthritis and arthralgia are two different complications, therefore they should be mentioned separately in the recommendations.
NHS England	Short		1.5.3	- As a paediatrician, it is surprising that the recommendation suggests that adults can be seen every 3 to 6 months as surely only the most mild adults would be seen as infrequently as twice a year.	Thank you for your comment. The reviews in this recommendation are routine reviews as opposed to the more comprehensive annual, or bi-annual reviews conducted by the MDT. To guide the audiences reading the recommendation, the committee gave some examples of routine review frequency for different age groups, with frequency decreasing with age. The ranges of frequencies provided in the recommendation are not mandatory, only examples, and should be tailored to the individual with cystic fibrosis. A greater description of the committee's discussion on this area is provided in the full guideline section titled "evidence to recommendations"
NHS England	Short		1.6.2	The recommendation notes that lung function testing can be done by children and young people who can do this. It would be worth mentioning that this is usually from 5-6 years of age.	Thank you for your comment. The committee discussed your comment and decided not to mention a usual minimum age because it would be up to the paediatrician's judgement to decide who is able to do lung function testing with spirometry. This has now been specified in the "Evidence to recommendations" section in the full guideline.
NHS England	Short		1.6.3	It is controversial to suggest 'consider measuring lung clearance index (LCI) at each routine review if spirometry is normal'. There are huge numbers of children who have normal lung function and it would be inappropriate for them to have LCI every time in clinic, given the length of time the test takes in each individual and if one adds in the time taken to clean equipment between patients, it would be impossible logistically for this to be carried out. It is also certainly not clear whether there is any evidence that it is a useful thing for routine review in every clinic. The committee then actually put usefulness of LCI as one of their recommendations for research (page 34) therefore I feel it is inappropriate to put this in as a major recommendation.	Thank you for your comment. The recommendation has now been amended to state "at a routine review" rather than "at each routine review". The section "Evidence to recommendations" in the full guideline has now been modified to mention that no evidence was found on LCI. In the same section it is noted that LCI is currently in its infancy in the UK, but could provide additional respiratory information to spirometry. As a result the committee made recommendations to consider the use of LCI for those clinics that have access to the equipment and ability to interpret the results. The recommendation states to "consider" measuring LCI, which means that health care professionals would consider whether to do so based on their clinical judgement. To enable stronger recommendations in the future, a research recommendation to assess if LCI is a useful and cost-effective tool for the routine assessment and monitoring of changes in pulmonary status in people with cystic fibrosis was prioritised by the committee.
NHS England	Short		1.6.4	The recommendation on respiratory secretions for microbiology refers to including mycobacteria but this should be termed non- tuberculosis mycobacteria.	Thank you for your comment. The committee discussed your comment and agreed that non-tuberculous was the right term, so the recommendation has been amended to state non-tuberculous mycobacteria.
NHS England	Short		1.6.6	The recommendation notes that people with CF with lung disease who have symptoms that are concerning the family members or carers, as well as the healthcare professional, can decide whether remote telemedicine or face to face assessment is needed. They then suggest a number	Thank you for your comment. The committee discussed your comment and noted that some people have devices that allow them to measure oxygen saturation and FEV1, and take respiratory secretion samples, at home. Many people would be able to measure weight and

				of assessments to consider, all of which would need face to face assessment apart from the review of the part history. This needs clarification.	length or height at home, and clinical history could be reviewed using telemedicine. Therefore the committee agreed that the guideline should recommend to decide whether to provide a remote telemedicine or face-to-face assessment depending on the assessments that are needed. The section "Evidence to recommendations" in the full guideline has been modified to specify that these assessments could be performed at home.
NHS England	Short		1.6.7	This is a controversial recommendation which states 'think about doing a chest CT for children with CF who have not had one before to detect features that other tests would miss (for example, early bronchiectasis)'. If one takes this recommendation literally, it would suggest that every child should have a CT scan. The recommendation should be more specific as to which children and how often this should be done because the majority of children do not require a CT chest scan and the radiation issue has never been resolved properly in terms of future cancer risk, given they may have repeated CT scans. This is not to say that no child should have a CT scan, as obviously there are a number of clinical circumstances in which this is an important investigation but this should not be routine because one has not been done before.	Thank you for your comment. The recommendation has been amended to specify low-dose CT scan. The committee noted that the recommendation states to think about a low-dose chest CT scan rather than stating to perform this on any child that has not had a CT scan before. Therefore, performing the CT scan would be subject to clinical judgement based on individual circumstances. This has now been explained in the section "Evidence to recommendations" in the full guideline.
NHS England	Short		1.6.10	There is a discussion about using bronchoalveolar lavage to obtain airway samples in children and young people under certain situations. The recommendation does not mention the use of induced sputum which as an increasingly useful technique in children, including those at quite a young age, and it avoids the need for general anaesthetic and bronchoscopy with a relatively simple outpatient procedure.	Thank you for your comment. The recommendation has been amended to mention sputum induction as an example of non-invasive upper airway respiratory secretion sampling, which would be performed before thinking about broncho-alveolar lavage.
NHS England	Short		1.6.11	The recommendation on airway clearance technique requires comment from the physiotherapy group. The recommendation is vague and recommends discussing the use of airway clearance techniques with people with CF who do not have lung disease. It is likely that all children with CF do have lung disease to a degree which has been well shown in studies in London and Australia looking at CT scans, lavage for inflammation and infant lung function and LCI. It is standard protocol for all children to have routine physiotherapy. The next section (1.6.12) to offer training in airway clearance techniques for children who have lung disease should go with the above recommendation so this could be amended to state that all parents should be offered training in airway clearance techniques.	Thank you for your comment. The recommendations have now been amended. The guideline now recommends to discuss the use of airway clearance techniques with people with cystic fibrosis who do not have clinical evidence of lung disease and their parents or carers (as appropriate) and to provide them with training in airway clearance techniques and to explain when to use them. A separate recommendation states to offer training in airway clearance techniques to people with cystic fibrosis who have clinical evidence of lung disease and their parents or carers (as appropriate). The recommendation on people with no clinical evidence of lung disease has been kept separate from the recommendation on people with clinical evidence of lung disease because the former may not have to use airway clearance techniques on a regular basis. However training on airway clearance techniques should cover ways to identify the need for performing these techniques. This would allow people with cystic fibrosis to start independently when appropriate rather than delaying the use of these techniques until a health care professional has identified the need. On the other hand, the committee agreed that when a patient has clinical evidence of lung disease or has received a treatment that produces sputum, such as mucolytic treatment, performing airway clearance techniques on a regular basis has a strong rationale and is often helpful in relieving symptoms of cough and breathlessness.
NHS England	Short		1.6.15	The recommendation says do not offer high frequency chest wall oscillation as an airway clearance technique. On principle, this is fine but would suggest it should say 'Do not routinely offer; this as there are exceptional circumstances in which case this form of physiotherapy is necessary, for example, children with autism who will not allow manual percussion.	Thank you for your comment. We have amended the recommendation to consider the use of high frequency chest wall oscillation in exceptional clinical circumstances as determined by the specialist CF team. The section on evidence to recommendations in the full guideline explains that the CF team would use the NHS definition of exceptional clinical circumstances.
NHS England	Short		1.6.16	The recommendation suggests using non-invasive ventilation to help with airway clearance techniques in people who have moderate or severe lung disease. It is a useful technique in those with severe lung disease but generally, those with moderate are most unlikely to need this and even more so unlikely to carry it out at home.	Thank you for your comment. Based on their experience and expertise, the committee noted that NIV could be used in people with cystic fibrosis who have moderate or severe lung disease and cannot clear their lungs using standard airway clearance techniques. This is because it is known that NIV unloads the respiratory muscles, therefore, it reduces the symptoms associated with respiratory muscle fatigue in moderate and severe lung disease such as reduced oxygen and breathlessness. The Committee also agreed that NIV can be beneficial as a short-term option in moderate disease, when people have difficulty clearing their airways using other clearance techniques, by unloading the respiratory muscles and reducing fatigue. The recommendation on NIV has been modified accordingly.
NHS England	Short		1.6.17	The recommendation suggests offering a mucoactive agent to people with CF who have respiratory symptoms or other evidence of lung disease. The European Cystic Fibrosis Society and the US Guidelines suggest offering mucoactive agents (Pulmozyme) to all children aged 6 years and above. Is there is a reason that the NICE Guidelines differ from these recommendations.	Thank you for your comment. The recommendation has been amended to refer to clinical evidence of lung disease rather than respiratory symptoms or other evidence of lung disease. As explained in the full guideline under "Consideration of clinical benefits and harms", the committee discussed whether a mucoactive or mucolytic agent should be prescribed to everyone who has cystic fibrosis. However, taking into account the potential adverse effects, as well as the inconvenience and the cost of treatment, it was agreed not to recommend it to everyone; instead, the Committee agreed that it should be offered to people with cystic fibrosis who have clinical evidence of lung disease.
NHS England	Short		1.6.22	The recommendation suggests that flucloxacillin prophylaxis should be given to children and consider continuing in up to 6 years of age. This is quite old now and is not standard UK practice and 2-3 years of age far more likely to be the current recommendation.	Thank you for your comment. The recommendation has been amended to state to offer flucloxacillin as antibiotic prophylaxis against respiratory *Staphylococcus aureus* infection from the point of diagnosis up to age 3, and to consider continuing up to 6 years of age. The rationale for these age cut-offs has been added to the full guideline in the "Evidence to recommendations" section. The committee noted that a beneficial effect (decreased number of children in whom *S aureus* was isolated) was observed for the comparison oral flucloxacillin versus placebo + antibiotic "as required" at 2 and 3 years of follow-up. There was no evidence on flucloxacillin after 3 years. Therefore, the committee recommended to offer flucloxacillin up to age 3. The committee noted that the same beneficial effect was observed for the comparison between another anti-

					staphylococcal agent (oral cephalexin) versus placebo + antibiotic “as required” at each subsequent year of follow-up up to 6 years of follow-up. Although this evidence was on an anti-staphylococcal agent, it was not specifically on flucloxacillin therefore the committee decided to only make a weak recommendation to “consider” continuing flucloxacillin up to 6 years of age.
NHS England	Short		1.6.27	The recommendation reads ‘do not routinely use antibiotics to suppress MRSA in people with stable pulmonary disease’. This is no mention here that certainly all children who have MRSA grown in respiratory secretions would have an attempt at eradication for this, with oral antibiotics and skin disinfectant treatment. This should be clarified as the suggestion from 1.6.28 is to treat if the patient us unwell with a pulmonary exacerbation or has decline in lung function.	Thank you for your comment. Some of the recommendations on MRSA have been modified. A new recommendation states that for people of new evidence of MRSA respiratory infection (with or without pulmonary exacerbation), specialist microbiological advice should be sought on treatment to eradicate it. A separate recommendation states that antibiotics should not be routinely used to suppress chronic MRSA in people with stable pulmonary disease. A third recommendation states that specialist microbiological advice should be sought if a person with cystic fibrosis and chronic MRSA respiratory infection becomes unwell with a pulmonary exacerbation or shows a decline in pulmonary function.
NHS England	Short		1.6.30	This is not standard practice. Whilst people will continue with inhaled antibiotics, certain patients do not receive extended courses of oral. The same follows for if they are clinically unwell.	Thank you for your comment. The section "Evidence to recommendations" in the full guideline explains that If the person is clinically well, the committee suggested it should be treated in order to try to eradicate it using a combination of systemic antibiotics, oral or intravenous, with an inhaled antibiotic. They discussed the use, for example, of oral ciprofloxacin combined with inhaled colistin or nebulised tobramycin. The recommendation to treat this group was based on the committee’s recognition that *P aeruginosa* is an important pathogen in cystic fibrosis. In their expert opinion intensive treatment with systemic and inhaled antibiotics should improve the chances of eradication. The committee made this recommendation based on their clinical experience as the available evidence was scarce and of very low quality and, therefore, not very useful in making recommendations. If the person is clinically unwell, for example with new respiratory symptoms and signs or a worsening of existing respiratory symptoms and signs, the approach might be different. The committee recommended that, in that situation, the initial therapy should consist of a course of intravenous antibiotics with an inhaled antibiotic. They discussed, for example, the use of 2 anti-pseudomonal antibiotics, such as ceftazidime and tobramycin, given intravenously together with the inhaled antibiotic. This recommendation is based on moderate quality evidence that showed participants who received an inhaled antibiotic in addition to a combination of 2 intravenous antibiotics were less likely to be admitted to hospital due to a pulmonary exacerbation. In both groups, based on the consensus of the committee, they advised giving extended treatment in order to try to increase the likelihood of eradication.
NHS England	Short		1.6.35	- The recommendation suggests that if patients have deteriorated despite regular inhaled colistimethate sodium, consider nebulised Aztreonam or nebulised Tobramycin or Tobramycin DPI. NHS England policy states that Tobramycin is second line and Aztreonam is third line – this is based on acquisition cost and should be reflected in the NICE Guideline. - It would also be worth mentioning the use of inhaled Levofloxacin which is in the late stage of NHS England recommendation process where once finalised, will be offered as a fourth line inhaled antibiotic for adults and by the time the NICE Guidelines are published, the Levofloxacin recommendation will be published.	Thank you for your comment. The cost-effectiveness of aztreonam was assessed during guideline development. The additional benefits associated with aztreonam were found to outweigh its additional cost compared to nebulised tobramycin. The results of the cost-effectiveness analysis and the committee's discussion on those results can be found in the full guideline and appendix k. Levofloxacin was not included in the protocol for this review, as a result, recommendations were not be made.
NHS England	Short		1.6.38	The recommendation suggests that a patient with B/cepacia whether clinically well or not would have eradication with intravenous antibiotics. There are circumstances quite often in children where they are extremely well in which care oral eradication treatment is attempted.	Thank you for your comment. The committee discussed your comment and decided to keep the recommendation to use a combination of intravenous antibiotics, because this treatment would be quicker and more likely to eradicate the infection.
NHS England	Short		1.6.44-48	Non-tuberculosis mycobacteria has been put together in these recommendations and that is unhelpful. There is quite a difference in approach and management of those with M abscesses and those with MAI o MAC and these should be differentiated in the recommendations as they are in the European/US guidelines.	Thank you for your comment. The committee decided not to make more detailed recommendations because no evidence was found on nun-tuberculous mycobacteria. However recommendations on this pathogen have now been amended to state to seek specialist microbiological advice on which antibiotics to use and on the duration of treatment. Moreover, the section "Evidence to recommendations" in the full guideline states that the committee noted that there was existing consensus guidance on the management of non-tuberculous mycobacteria in a publication by Floto et al. (2016) titled “US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis” (http://thorax.bmj.com/content/71/Suppl_1/i1)
NHS England	Short		1.6.54	The recommendation suggests that if Azithromycin has not helped, to consider oral corticosteroids and this is controversial given long term oral steroids are associated with side effects and this is generally not a treatment that is undertaken.	Thank you for your comment. The Committee agreed that oral corticosteroids may be a suitable alternative for some patients if azithromycin is ineffective, which is why a recommendation to "consider" their use was made. In the "Evidence to recommendations" section in the full guideline it is noted that tolerability and side effects of oral corticosteroids should be revised regularly. The cost and quality of life decrements associated with treatment related adverse effects were also included in the economic model that was developed for this review.
NHS England	Short		1.7.5	The recommendation suggests that tests for exocrine pancreatic insufficiency should be repeated annually in children and young people if the initial result is normal. It will usually be repeated once or twice in a baby with a normal level, but usually this would only be repeated if symptoms suggest rather than routinely every year.	Thank you for your comment. We have removed the bullet that suggests the test is repeated annually, and amended the recommendation to state that the test should be repeated if symptoms or signs suggesting malabsorption occur at any age.
NHS England	Short		1.7.10	In discussing acute onset of abdominal pain with no features of DIOS, they suggest abdominal ultrasound or abdominal CT scan. This should mention that one would consider a surgical opinion at that point as well, particularly in children.	Thank you for your comment. The committee discussed your suggestion but decided not to include to consider a surgical opinion in the recommendation. The committee agreed that a surgical opinion would only be consulted after the diagnostic tests if there was diagnostic uncertainty. Moreover, the committee also recommended to consider surgery as a last resort,

					after first-line treatment - diatrizoate meglumine and diatrizoate sodium solution (Gastrografin), and second-line treatment - an iso-osmotic polyethylene glycol and electrolyte (PEG) solution (Macrogols), if prolonged treatment with a PEG solution is not effective.
NHS England	Short		1.7.15	The recommendation suggests considering surgery as a last resort for DIOS if not responding to treatment. This should also discuss the role of colonoscopy and gastroenterology as well.	Thank you for your comment. The committee agreed that the recommendation to manage suspected distal intestinal obstruction syndrome with supervision from specialists who have expertise in recognising and treating the condition and its complications indirectly referred to specialty areas such as colonoscopy and gastroenterology. The committee discussed your suggestion and decided not to specifically mention the role of colonoscopy and gastroenterology in the recommendations not to make them too detailed. However, the section "Evidence to recommendations" has now been modified to specify that the expertise of specialists who supervise management of suspected DIOS should also cover the specialty areas of colonoscopy and gastroenterology.
NHS England	Short		1.7.18	The recommendation mentions the use of liver ultrasound if liver function tests were abnormal. There is no discussion of any role of liver ultrasound screening for liver disease in children.	Thank you for your comment. The committee discussed your comment and decided not to recommend routine ultrasound screening for liver disease because the evidence did not support this. The recommendations state to perform a clinical assessment and liver function blood tests at the annual review. The committee agreed that decisions on the tests to be included in the clinical assessment should be made at individual centres using clinical judgement. This means that individual centres would not be prevented from including an ultrasound scan at annual review. The committee noted that it is currently common practice to perform blood test investigations to look for evidence of liver disease. The committee recognised that ultrasound can detect evidence of liver disease, for example changes in liver echogenicity as well as advanced changes suggestive of portal hypertension. It can also detect the presence of gallstones which sometimes occur in cystic fibrosis. Ultrasound scanning is commonly used to monitor cystic fibrosis-related liver disease. The committee agreed that this may not be necessary if there was no evidence of liver disease, but a liver ultrasound scan should be performed if the blood liver function tests were abnormal. This has now been clarified in the "Evidence to recommendations" section in the full guideline.
NHS England	Short		1.7.28	The recommendation discusses the use of DXA bone scans but does not mention any role of routine screening in children.	This has now been clarified in the "Evidence to recommendations" section in the full guideline.
NHS England	Short		1.8.5	The recommendation suggests separating people with CF with intermittent pseudomonas during outpatient clinics. This fails to take into account that very often the clinician does not know what a children growing, as they may only be able to have a cough swab and are not producing sputum. Furthermore, it is not possible to tell if a child has had pseudomonas until the culture result comes back showing that they had had it, in the clinical having previous not had it. This means that all children need to be segregated from each other at all times, rather than by organism.	Thank you for your comment. The recommendations on cross-infection have now been amended to recommend to separate people individually both in the outpatient and inpatient setting. Moreover, the recommendations now state "have intermittent isolation of *Pseudomonas aeruginosa*" rather than "have intermittent *Pseudomonas aeruginosa*". The committee agreed that even if a clinic separates all people from each other, casual contact may still occur. Therefore, the committee agreed that a combination of cohorting and individual segregation was more effective than individual segregation alone, and recommended that the local infection control strategy that covers outpatient and inpatient care should include cohorting. However, given the lack of evidence supporting segregation based on intermittent *P aeruginosa*, and considering the difficulties involved in diagnosing intermittent *P aeruginosa*, the committee decided not to be overly prescriptive and recommended to "consider" keeping people who have intermittent isolation of *P aeruginosa* separate from people who do not have this infection, for example by using separate outpatient clinics. "Consider keeping" people separate is a weaker recommendation than recommending to "keep" people separate and any considerations would have to be made based on clinical judgement.
Oxford Adult Cystic Fibrosis Centre	Full	176	31	CF specialist nurses commonly undertake a much wider role than implied in this guideline. CF specialist nurses in our unit are involved in the clinical assessment of the unwell CF patient, are often non-medical prescribers, deliver trials of nebulised medications, administer and monitor home courses of IV antibiotic therapy in addition to the roles suggested in the guideline. Greater recognition of the extended scope of CF nursing roles is advised.	Thank you for your comment. Some examples about thehe clinical role of a specialist nurse have now been included in the recommendation.
Oxford Adult Cystic Fibrosis Centre	Full	176	31	Although a social worker is included in the core members of the CF MDT, there is no recommendation on the role and scope of practice for the CF social worker.	Thank you for your comment. Thank you for your comment. A recommendation has been added to the section on the multidisciplinary team to include some examples about the role of the social worker as part of the MDT. These include adjusting to long term treatment but also support and advice relating to education or employment.
Oxford Adult Cystic Fibrosis Centre	Full	18	26	The role of CFTR modulators is not included either in what is or is not covered by the guideline. This is a fairly major omission and will limit the usefulness of the guideline.	Thank you for your comment. CFTR modulators were not included in the scope as current clinical practice in this area was considered to be consistent and effective, relative to the other areas under consideration. For completeness, a recommendation referring to the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation has been added.
Oxford Adult Cystic Fibrosis Centre	Full	530	17-24	Line 17-24 feels out of place as they sound like concluding statements when further exploration of enteral feeding and appetite stimulants follow from these paragraphs. As a result this section does not flow logically.	Thank you for your comment. These paragraphs have been deleted from the full guideline.

Oxford Adult Cystic Fibrosis Centre	Full	531	18	Line 18 refers to supplement costs of £4.36 and that is based on Calogen. This supplement is not reflective of first line supplements used in CF.	Thank you for your comment. The supplement has been changed to Scandishake in the section you refer to.
Oxford Adult Cystic Fibrosis Centre	Full	672	General	The discussion and recommendations offer no advice on the risk or management of potential cross-infection with Mycobacterium abscessus. This issue is of considerable concern to the CF community and deserves more careful consideration in this document.	Thank you for your comment. The recommendations specific to *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex were based on the clinical and economic evidence identified. The committee did not make recommendations specific to *Mycobacterium abscessus* because no evidence was identified to make recommendations in addition to those that were not pathogen specific. All recommendations in this section except for those two that refer to *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex should apply to all people with cystic fibrosis, including those with *Mycobacterium abscessus*. This has now been explained in the section "Evidence to recommendations" in the full guideline.
Oxford Adult Cystic Fibrosis Centre	Short	11	25	Routine review for adults with CF is recommended “every 3 or 6 months” in this section but in Section 1.6.1 review is recommended “at least every 3 months.” This advice should be consistent.	Thank you for your comment. The committee recommended routine reviews at least every 3 months for adults with cystic fibrosis with clinical evidence of lung disease. A separate recommendation relating to the general population of adults with cystic fibrosis mentions an example of frequency of 3 to 6 months. As explained in the section "Evidence to recommendations", frequency of routine reviews would vary based on individual needs, therefore "3 to 6 months" is given as an example rather than as a standard to be followed for all adults. Given that the recommendation states “for example”, it does not prevent more frequent or less frequent reviews and does not contradict any other routine review timetables in the guideline.
Oxford Adult Cystic Fibrosis Centre	Short	20	12-21	There is a typo in the spelling of “*Haemophilus influenzae*” throughout – needs an e on the end.	Thank you for your comment. We have corrected the spelling of *Haemophilus influenzae* throughout.
Oxford Adult Cystic Fibrosis Centre	Short	22	26-27	Does the recommendation on inhaled corticosteroids need clarification for those patients with coexisting CF and asthma?	Thank you for your comment. The committee agreed it would be inappropriate to amend the recommendation for asthma as this would not be treated using an immunomodulatory dose.
PARI Medical Ltd.	Full	263	32	This is an example line reference; please delete the word ‘mask’ – most patients using PEP therapy in the UK do so using a mouthpiece. In our view following PEP with the word ‘device’ rather than ‘mask’ would be a more appropriate. Perhaps using this more neutral expression throughout the document would more accurately reflect the practice of HCPs we encounter.	Thank you for your comment. We have deleted the term "mask" from this paragraph, from a few included studies, from the comparison headings and from the section linking evidence to recommendations.
PARI Medical Ltd.	Full	General	General	We are concerned that this recommendation may underrepresent the management and care of the upper airways with sinonasal nebuliser developments in order to offer the most appropriate delivery systems. The CF Trust recently published an updated guideline: “Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis” . • It was published on 25th April 2017. • It can be found here: https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-care/consensus-documents Section 6 specifically includes management of the upper airways & section 6.3 specifically includes the use of delivery systems for sinonasal inhalation of vibrating aerosols (PARI Sinus nebuliser); we believe that the new NICE guidance should also include the therapeutic option with vibrating aerosols (e.g. with the PARI Sinus device) for upper airway management.	Thank you for your response. Management of the upper airways was not part of the scope of this guideline. In section "What the guideline is about" of Appendix A: Scope, it is specified that the guideline does not cover "Specialist management of cystic-fibrosis-related ear, nose and throat (ENT) disorders".
PARI Medical Ltd.	Full	General	General	In cystic fibrosis very often the upper airways are involved. The term of the “united airways” mainly developed by Hoiby et al puts emphasis to the fact that there is a very close relation between the upper and the lower airways. Upper and lower airways are in fact united to one system with overlapping diseases and symptoms [3a-f]. In CF chronic rhinosinusitis and nasal polyps are very common, bacterial infections of the paranasal cavities are additional threats. The patients’ quality of life and their overall health are relevantly impaired [1a-d]. Mucolytic agents as dornase alfa and isotonic (0.9%) as well as hypertonic (6%; 7%) saline solutions which are regularly used for the treatment of the CF lung can also be effectively in the upper airways. But the deposition of inhaled drugs into paranasal sinuses is substantially limited if traditional nebulisers are used. With the PARI SINUS™ nebuliser it has been shown in deposition studies that the administration of aerosols in the paranasal sinuses is possible[4a-d]. In CF the antibiotics Colistin and Tobramycin are widely used for the treatment of pseudomonas aeruginosa or staphylococcus aureus infections in the lower respiratory tract. Recent publications show that the upper airways are often colonized with bacteria of the same genotype than the lower airways. Hence, a comprehensive treatment of upper and lower airways seems to be	Thank you for your response. Management of the upper airways was not part of the scope of this guideline. In section "What the guideline is about" of Appendix A: Scope, it is specified that the guideline does not cover "Specialist management of cystic-fibrosis-related ear, nose and throat (ENT) disorders". The committee noted that there was more clinical uncertainty about management of lower airways therefore this was prioritised in the scope. With regards to your comment about the PARI SINUS™ nebuliser, different agents were compared in the mucoactive and antimicrobials review, however comparisons within agents to compare delivery systems were not included as comparisons of interest in the protocol. The type of delivery system (when reported) was extracted from the included studies and is reported in appendix J. Thank you for suggesting these studies. The study by Wilson et al. (2014) is about eradication of paranasal sinus pathogens, which was out of the scope of this guideline. The following studies do not evaluate interventions included within the scope of this guideline: DiCicco 2014, Ferril 2014, Mainz 2009, Charlson 2011, Goddard 2012, Lavin 2013. The following study was excluded from the review on mucoactive agents: Mainz 2014. The exclusion reason was “Data is poorly reported and cannot be pooled" (please see appendix H for lists of excluded studies). The following study is a literature (non-systematic) review and therefore was not eligible for inclusion in reviews in this guideline: Kang 2015.

				reasonable[4a-d]. The following literature shows the rationale for a concentrated approach in the treatment of upper airway problems in CF. 1. Overall role of Sinonasal complications /CRS. 181. Mainz JG et al. Sinonasal inhalation of dornase alfa administered by vibrating aerosol to cystic fibrosis patients: A double-blind placebo-controlled cross-over trial. J Cyst Fibrosis, 2014; 13(4), 461. 182. DiCicco M et al. Efficacy and tolerability of a new nasal spray formulation containing hyaluronate and tobramycin in cystic fibrosis patients with bacterial rhinosinusitis. J Cystic Fibrosis. 2014; 13(4), 455. 183. Ferril GR et al. Comparison of radiographic and clinical characteristics of low-risk and high-risk cystic fibrosis genotypes. Int Forum Allergy Rhinol. 2014; 4:915-920. Mainz JG, Naehrlich L, Schien M, Kading M, Schiller I, Mayr S, Schneider G, Wiehlmann L, Cramer N, Pfi ster W, Kahl BC, Beck JF, Tummler B. Concordant genotype of upper and lower airways P.aeruginosa and S.aureus isolates in cystic fi brosis. Thorax 64: 535-540, 2009 2. Validation via SNOT Score. Relevant publications: 184. Kang SH et al. Chronic rhinosinusitis and nasal polyposis in cystic fibrosis: update on diagnosis and treatment. Jornal brasileiro de pneumologia : publicaça?o oficial da Sociedade Brasileira de Pneumologia e Tisilogia, Jan 2015; vol. 41, no. 1, p. 65-76. Concept of united airways: Hoiby, N., B. Frederiksen, and T. Pressler. “Eradication of Early Pseudomonas Aeruginosa Infection.” J Cyst Fibros 4, no. suppl 2 (2005): 49–54. Wilson P et al. Paranasal sinus pathogens in children with cystic fibrosis: Do they relate to lower respiratory tract pathogens and is eradication successful? J Cyst Fibrosis 13 (2014) 449-454. Charlson ES, Bittinger K, Haas AR, Fitzgerald AS, Frank I, Yadav A, Bushman FD, Collman RG. Topographical continuity of bacterial populations in the healthy human respiratory tract. Am J Respir Crit Care Med 184: 957-963, 2011 Goddard AF, Staudinger BJ, Dowd SE, Joshi-Datar A, Wolcott RD, Aitken ML, Fligner CL, Singh PK. Direct sampling of cystic fi brosis lungs indicates that DNA-based analyses of upper-airway specimens can misrepresent lung microbiota. Proc Natl Acad Sci U S A 109: 13769-13774, 2012 Lavin J, Bhushan B, Schroeder JW Jr. Correlation between respiratory cultures and sinus cultures in children with cystic fi brosis. Int J Pediatr Otorhinolaryngol 77: 686-689, 2013 Mainz JG, Naehrlich L, Schien M, Kading M, Schiller I, Mayr S, Schneider G, Wiehlmann L, Cramer N, Pfi ster W, Kahl BC, Beck JF, Tummler B. Concordant genotype of upper and lower airways P.aeruginosa and S.aureus isolates in cystic fi brosis. Thorax 64: 535-540, 2009 Pulsating aerosol / PARI SINUS as treatment option 181. Mainz JG et al. Sinonasal inhalation of dornase alfa administered by vibrating aerosol to cystic fibrosis patients: A double-blind placebo-controlled cross-over trial. J Cyst Fibrosis, 2014; 13(4), 461. Mainz JG, Michl R, Pfi ster W, Beck JF. Cystic Fibrosis Upper Airways Primary Colonization with Pseudomonas aeruginosa: Eradicated by Sinonasal Antibiotic Inhalation. Am J Respir Crit Care Med 184: 1089-1090, 2011b Mainz JG, Hentschel J, Schien C, Cramer N, Pfi ster W, Beck JF, Tummler B. Sinonasal persistence of Pseudomonas aeruginosa after lung transplantation. J Cyst Fibros 11: 158-161, 2012 Info aus dem “Economic Dossier für PARI SINUS / France”? (let me know if you need more on this) Economic value arguments can especially rely on: The role of UAWs as a bacterial reservoir;	This study on eradication of early *Pseudomonas aeruginosa* infection was not a randomized controlled trial and therefore not eligible for inclusion: Hoiby 2005. The following study is about a case report and therefore not eligible for inclusion in reviews in this guideline: Mainz 2011b. The following study reports on 2 case reports therefore would not be eligible for inclusion in reviews for this guideline: Mainz 2012.

				The impact of UAW nebulization on P. aeruginosa infection The importance of P. aeruginosa in the prognosis and treatment costs of CF patients	
Profile Pharma	Full	453	13-25	The Pari e-flow is mentioned as a fast nebuliser. The I-neb has similar or better treatment times with the added advantage of recording when it is used and so monitors adherence.	Thank you for your comment. The I-neb has been added as another example.
Profile Pharma	Full	658	37	Only the I-neb can currently measure adherence electronically	Thank you for your comment. The review question on psychological assessment evaluated methods of assessment of adherence to drug treatment and used electronic monitoring of adherence or pharmacy records as the reference standards. One included study (Daniels 2011) compared the index tests of self-report and clinician-report to the reference standard of electronic monitoring with the I-neb nebulizer system. Another study (Siracusa 2015) compared the index tests of self-report and pharmacy refill history to the reference standard of electronic monitoring with the Medication Event Monitoring System (MEMS). The evidence statements from both studies mention that there was an overestimation of adherence by the index tests compared to the reference standards. The section "Evidence to recommendations" in the full guideline has been modified and it now states that the committee noted that adherence is extremely difficult to measure in both clinical practice and research, unless a particular objective measuring tool is employed (for example electronic monitoring or pharmacy records), which is rare in routine clinical practice. The committee noted that the I-neb is by far the commonest method of electronic monitoring in the UK. The committee stressed that adherence problems are common in people with chronic conditions, and those with a number of concurrent treatments, and are not specific to cystic fibrosis. They agreed that the overarching principles from the NICE guidance on Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence [CG76] is applicable to people with cystic fibrosis. Therefore, the committee decided not to make a recommendation specific to measuring adherence in cystic fibrosis care.
Profile Pharma	Full	668	44-45	The I-neb can objectively measure adherence	Thank you for your comment. The review question on psychological assessment evaluated methods of assessment of adherence to drug treatment and used electronic monitoring of adherence or pharmacy records as the reference standards. One included study (Daniels 2011) compared the index tests of self-report and clinician-report to the reference standard of electronic monitoring with the I-neb nebulizer system. Another study (Siracusa 2015) compared the index tests of self-report and pharmacy refill history to the reference standard of electronic monitoring with the Medication Event Monitoring System (MEMS). The evidence statements from both studies mention that there was an overestimation of adherence by the index tests compared to the reference standards. The section "Evidence to recommendations" in the full guideline has been modified and it now states that the committee noted that adherence is extremely difficult to measure in both clinical practice and research, unless a particular objective measuring tool is employed (for example electronic monitoring or pharmacy records), which is rare in routine clinical practice. The committee noted that the I-neb is by far the commonest method of electronic monitoring in the UK. The committee stressed that adherence problems are common in people with chronic conditions, and those with a number of concurrent treatments, and are not specific to cystic fibrosis. They agreed that the overarching principles from the NICE guidance on Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence [CG76] is applicable to people with cystic fibrosis. Therefore, the committee decided not to make a recommendation specific to measuring adherence in cystic fibrosis care. Another paragraph in the "Evidence to recommendations" section has been modified to state that The committee noted that the reference standards for measuring adherence are electronic monitoring or pharmacy records, and noted that the I-neb is the most commonly used method of electronic monitoring in the UK.
Profile Pharma	Full	General		The importance of adherence is emphasised throughout the document. At present only one device can objective measure true adherence as it records each time it is used. This is the I-neb nebuliser.	Thank you for your comment. The review question on psychological assessment evaluated methods of assessment of adherence to drug treatment and used electronic monitoring of adherence or pharmacy records as the reference standards. One included study (Daniels 2011) compared the index tests of self-report and clinician-report to the reference standard of electronic monitoring with the I-neb nebulizer system. Another study (Siracusa 2015) compared the index tests of self-report and pharmacy refill history to the reference standard of electronic monitoring with the Medication Event Monitoring System (MEMS). The evidence statements from both studies mention that there was an overestimation of adherence by the index tests compared to the reference standards. The section "Evidence to recommendations" in the full guideline has been modified and it now states that the committee noted that adherence is extremely difficult to measure in both clinical practice and research, unless a particular objective measuring tool is employed (for example electronic monitoring or pharmacy records), which is rare in routine clinical practice. The committee noted that the I-neb is by far the commonest method of electronic monitoring in the UK. The committee stressed that adherence problems are common in people with chronic conditions, and those with a number of concurrent treatments, and are not specific to cystic fibrosis. They agreed that the overarching principles from the NICE guidance on Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence [CG76] is applicable to people with cystic fibrosis. Therefore, the committee decided

					not to make a recommendation specific to measuring adherence in cystic fibrosis care.
Roche Products Limited	General	General		As a registered stakeholder we can confirm that we have no additional comments on the consultation document.	Thank you for your comment.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	290	14-22	NIV is used in 4-5% of the adult population (UK registry report 2015) It is also used as an adjunct to physiotherapy, this has been omitted	Thank you for your comment. The full guideline has now been amended. The sentence stating that NIV is not widely used in clinical practice has been deleted. The review protocol on airway clearance (appendix D) did not prioritise combinations of interventions, therefore evidence on NIV used as an adjunct to other airway clearance techniques was not assessed for inclusion in the review. As a result, the guideline does not make reference to this, Based on their experience and expertise, the committee noted that NIV could be used in people with cystic fibrosis who have moderate or severe lung disease and cannot clear their lungs using standard airway clearance techniques. The recommendation on NIV has been modified accordingly. The committee looked at the data on NIV use in the UK CF Registry 2015 Annual Data Report (CF Trust 2016), however the committee decided not to include this data in the full guideline because the report does not specify the purpose of NIV and the committee believed that the data referred to NIV use for nocturnal hypoventilation; therefore this data might be confusing in the section on airway clearance.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	292	8	The High frequency oscillation Vest – the evidence is that it is inferior to some other physiotherapy techniques, however, this does not mean it should be recommendation never to use it. It is frequently used in the UK as an adjunct to other techniques and the evidence is not strong enough to say “never” use	Thank you for your comment. Moderate quality evidence from 2 trials showed that PEP was better at reducing pulmonary exacerbations. Based on this, the committee agreed that given the current evidence high frequency chest wall oscillation (HFCWO) should not be recommended as part of this guideline. No evidence on HFCWO as an adjunct to other airway clearance techniques was reviewed. However, the recommendation has been amended to consider the use of high frequency chest wall oscillation in exceptional clinical circumstances as determined by the specialist CF team and following the NHS England policy in individual funding requests. The full guideline explains that the CF team would use the NHS England definition of exceptional clinical circumstances.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	658	18-29	Strengths and Difficulties Questionnaire (SDQ) is neglected here as a tool – this a well validated, widely used tool useful for screening across emotional, behavioural and social dimensions in children from ages 4 -17 – should have been included in the review.	Thank you for your comment. The Strengths and Difficulties Questionnaire (SDQ) was not prioritised by the committee in the review protocol. The reason for this is that the SDQ is not universally accepted as a good tool for people with physical health conditions though it is a useful screen for use in general mental health practice.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	658	31-36	Far too “medical model” – particularly, because we have emphasised that clini psychs are embedded in the teams in the aspiration that there is prevention of the mental health disorder – in contradiction to this, only evidence of confirmed psychiatric diagnosis has been explored.	Thank you for your comment. For other psychological and behavioural problems listed in the protocol (such as school phobia), the reference standard was "as reported by the study" so the inclusion criteria went beyond confirmed psychiatric diagnosis.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	658	9-13	Comment 1: Missing – promote good psychological health (not just looking for problems). Comment 2: The clinical psychologist can also play a role in identifying whether other challenges of a psychological nature (e.g. enuresis, school absence) may be wholly or partially attributable to having a chronic health condition or not.	Thank you for your comment. The introduction has been modified to state that the role of the psychologist is to promoted psychological health. Moreover, the introduction now also states that the clinical psychologist can also play a role in identifying whether other challenges of a psychological nature (for example school absence or tics) may be wholly or partially attributable to having a chronic health condition or not. The example of enuresis was replaced by the example of tics in order to have an example relevant to both children and adults.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	658	6-8	And vice versa – emotional difficulties for other reasons can impact on CF treatments.	Thank you for your comment. The introduction has been modified to state that vice versa, emotional difficulties for other reasons can impact on CF treatments.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	658	3	Should instead state “Clinical Psychologist, with good links with the CF specialist MDT, can offer preventative model of working, by offering strategies to colleagues, patients and/or family and carers to explore their emotional wellbeing. If necessary the Clinical Psychologist can also offer further assessment and intervention, or facilitate onward referral for more intractable mental health difficulties which may, or may not, be attributable to the diagnosis of cystic fibrosis.	Thank you for your comment. The recommendations state that clinical psychologists are members of the MDT rather than external professionals with links to it. The introduction has been modified to replace the term core MDT with the term specialist CF MDT. Moreover, the introduction has been modified to state that clinical psychologists can offer a preventative model of working, by offering strategies to colleagues, patients or family and carers to explore their emotional wellbeing. If necessary the clinical psychologist can also offer further assessment and intervention, or facilitate onward referral for severe mental health conditions which may, or may not, be attributable to the diagnosis of cystic fibrosis.
Royal Brompton and Harefield Hospitals NHS Foundation	Full	658	6	Rather than “will be aware of” should be “Can hold in mind”	Thank you for your comment. We have amended the sentence to say "...can hold in mind any likely impact of cystic fibrosis treatments on emotional functioning…"

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Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	659	Table 3	EAT – no info re ages beyond “adolescents” – should give an age.	Thank you for your comment. The age (15 and over) for young people has been added to the table.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	660	Table 3	There is a cost to the questionnaires (e.g. PI-ED is approx. £1.00 per questionnaire) would be helpful to make sure this is in the health economic model. I think that the age range for the questionnaires should be documented .The ones I know are: • GAD-7- 16+ • PHQ((and I suppose from inference PHQ2) 16+ HADS -16+	Thank you for your comment. The cost of questionnaires has been added as a consideration in the full guideline. The age range for each questionnaire was added to the table in the full guideline. With regards to GAD-7, the full guideline now states that it is intended for use in adults but has been used in young people aged 13 and over. For HADS, PHQ-2 and PHQ-9, the full guideline now states that they are for use in adults and young people aged 13 and over.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	666	36-40	Suggest to delete everything from “They noted that even following transplant……” to end of that paragraph; and instead should highlight that adherence is extremely difficult to measure in both clinical practice and research, unless a particular objective measuring tool is employed (e.g. Daniels study-electronic measuring ,i-neb system), which is rare in routine clinical practice.	Thank you for your comment. The section "Evidence to recommendations" has now been modified to delete the section of the paragraph after "They noted that even following transplant" as suggested in your comment. Moreover, the same paragraph now states that the committee noted that adherence is extremely difficult to measure in both clinical practice and research, unless a particular objective measuring tool is employed (for example -electronic monitoring or pharmacy records), which is rare in routine clinical practice. The evidence used two different methods for electronic monitoring as reference standards to measure adherence: the I-neb was used in one study and the Medication Event Monitoring System (MEMS) was used in another study; however the committee noted that the I-neb is by far the commonest method for electronic monitoring in the UK. The committee stressed that adherence problems are common in people with chronic conditions, and those with a number of concurrent treatments, and are not specific to cystic fibrosis. They agreed that the overarching principles from the NICE guidance on Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence [CG76] is applicable to people with cystic fibrosis. Therefore, the committee decided not to make a recommendation specific to measuring adherence in cystic fibrosis care.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	667	30	Delete “ who are treatment compliant” and replace with “people with cystic fibrosis and/or their carers who are believed to be adherent to treatment, or where adherence is measured with objective measures (e.g. sweat test with use of Ivacaftor).	Thank for your comment. "who are treatment compliant" has been deleted to address your comment.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	668	18-20	Should be: “are more likely to be accepting of this role”	Thank you for your comment. We have amended the sentence to say "are more likely to be accepting of this role."
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	668	25 - 27	The team clinical psychologist can support the rest of the team in this by holding psychological wellbeing in mind, and supporting staff if they would like to think through the responses they get from patients (and or family members), and/or provide training to staff on ……	Thank you for your comment. The section "Evidence to recommendations" in the full guideline has been modified to state that the team clinical psychologist can support the rest of the team by holding psychological wellbeing in mind, and supporting staff if they would like to think through the responses they get from patients (or family members), or provide training to staff on delivery of basic emotional support.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	668	23-24	Should be recommendations. Very important for all MDT members to have a role in enquiring about a patient (or family member/carers) emotional wellbeing; with the clinical psychologist taking a lead in the MDT to support MDT members to do this confidently and safely, and offer additional clinical psychology level support when necessary.	Thank you for your comment. The committee discussed your comment about recommending informal but frequent “screening” by the psychologist and multidisciplinary team members by regularly asking questions about emotional wellbeing as well as physical health. The committee agreed that this should be covered in the section "Evidence to recommendations" in the full guideline rather than in the recommendations, because it is standard clinical practice to informally ask about a person's emotional wellbeing and physical health, especially with regular patients, and this is not specific to cystic fibrosis. The committee decided not to specify in the recommendations that the psychologist should support MDT members because it is expected of all members of an MDT that they would support each other through advice and consultation in relation to their respective areas of expertise.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	668	32	Should be: “Information provided to people with CF and/or their families/carers….”	Thank you for your comment. We have amended the sentence to "Providing information to people, and their family or carer, with cystic fibrosis…"

Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	668	33	Should not be "through self-referral"; should be "easy access to service, including self-referral"	Thank you for your comment. We have amended the sentence to say "easy access to services, including self-referral."
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Full	669	26	"A psychological screening should be offered as part of the annual review to all patients, families and carers. A referral for further assessment and intervention by this clinical psychologist or another mental health practitioner should be discussed with the patient/family and referral should be made if a serious mental health problem is identified. If this opportunity is declined by the patient/family, and this decision is considered to be to the detriment to the patient and or family members physical or mental health, then this necessitates discussion with the CF MDT with involvement of the safeguarding lead professionals.	Thank you for your comment. The committee discussed your suggestion to use the term "psychological screening" in the key conclusions of the "Evidence to recommendations" section and concluded that the term "assessment" was more appropriate as it was the term used in the recommendations. The recommendations use the term "assessment" rather than "screening" because "assessment" suggests a more individualised and flexible approach. This reflects the fact that no specific recommendations could be made regarding psychological assessment tools as no evidence was found. As explained in the full guideline, the committee highlighted there are no available tools specific to people with cystic fibrosis. For this reason, the committee made a research recommendation about the most effective measure of psychological functioning to use as a screening test for thresholds of concern in people with cystic fibrosis. The committee noted that, although assessment tools are helpful to assess the severity of the psychological or behavioural disorder, in practice psychologists are able to intervene without a formal diagnosis. Therefore, although a screening tool for psychological problems in cystic fibrosis would help, all people and families should be seen regularly by a psychologist who is able to perform assessments using clinical interview as well as screening measures. The committee discussed your suggestions relating to the referral process, however decided not to include this level of detail into the full guideline because discussions with the person or family about referrals, and how to proceed if this is declined by them, would not be specific to cystic fibrosis.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	General	General		There appears to be no reference to the TIDES study on anxiety and depression in the literature review	Thank you for your comment. The main aim of TIDES-CF were: • Estimate the prevalence of depression and anxiety in patients with CF ages 12 through to adulthood and parent caregivers of children with CF ages birth to 18. • Identify risk factors associated with symptoms of depression and anxiety. • Evaluate how depression and anxiety influence health outcomes (particularly number of exacerbations and hospitalizations, lung function and nutritional measures) (From website http://www.uclan.ac.uk/research/explore/projects/tides_cf.php). These aims do not match the inclusion criteria for the review question in this guideline "What strategies are effective at identifying people with cystic fibrosis for the presence of a psychological and/or behavioural problem?" Nevertheless, some studies performed under TIDES-CF were detected by the search and assessed for inclusion and exclusion. For example, this study was detected by the search: Latchford, G., Duff, A. J., Screening for depression in a single CF centre, Journal of Cystic Fibrosis, 12, 794-6, 2013. This study reports the results from the UK pilot study for TIDES in a single major CF centre. It was assessed for inclusion in the review and was excluded with the reason: "Compares two screening tools. No reference standard" (please see review protocol in appendix D and list of excluded studies in appendix H).
Royal Brompton and Harefield Hospitals NHS Foundation Trust	General	General		Flucloxacillin, no good evidence base to increase the current standard of care recommendation to use up until the age of 6 years. The only evidence is actually till 2 years (although current UK standard is to 3 years)	Thank you for your comment. The recommendation has been amended to state to offer flucloxacillin as antibiotic prophylaxis against respiratory *Staphylococcus aureus* infection from the point of diagnosis up to age 3, and to consider continuing up to 6 years of age. The rationale for these age cut-offs has been added to the full guideline in the "Evidence to recommendations" section. The committee noted that a beneficial effect (decreased number of children in whom *S aureus* was isolated) was observed for the comparison oral flucloxacillin versus placebo + antibiotic "as required" at 2 and 3 years of follow-up. Therefore, the committee recommended offering flucloxacillin up to age 3. The committee noted that the same beneficial effect was observed for the comparison between another anti-staphylococcal agent (oral cephalexin) versus placebo + antibiotic "as required" at each subsequent year of follow-up up to 6 years of follow-up. Although this evidence was on an anti-staphylococcal agent, there was no direct evidence on flucloxacillin after 3 years of follow-up. Therefore the committee decided to only make a weak recommendation to "consider" continuing flucloxacillin up to 6 years of age.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	10		P10 the list of complications is incomplete: pneumothorax, ABPA, hemoptysis. The bone disease is not osteoporosis.	Thank you for your comment. The protocol of the review on the prevalence of complications of cystic fibrosis did not prioritise these complications. Therefore the evidence on the prevalence of these complications was not reviewed and no recommendations were made on this. The committee noted that these are lower-respiratory complications of bronchiectasis or of severe lung disease, rather than complications of cystic fibrosis, and management of these complications is not different for people with cystic fibrosis. The recommendation on reduced bone mineral density has been amended to state to be aware that reduced bone mineral density (including osteoporosis) is common in people with cystic fibrosis.
Royal Brompton and Harefield Hospitals NHS Foundation	Short	11	1.5.3	4-weekly in 1st year of life too infrequent in first 6 months	Thank you for your comment. Based on their clinical experience and expertise, the committee agreed to recommend more frequent routine reviews after diagnosis and in early life. Following those initial years, the person's condition is likely to become more predictable. To guide the audiences reading the recommendation, the committee gave some examples of review frequency for different age groups, with frequency decreasing with age. The ranges of frequencies provided

Trust					in the recommendation are not mandatory, only examples, and should be tailored to the individual with cystic fibrosis. A greater description of the committee's discussion on this area is provided in the full guideline section titled "evidence to recommendations"
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	13	1.6.7	Ambiguous wording would imply we should be doing a CT on diagnosis at screening of newborns. Same page, CXR should mention ?pneumothorax or even if ABPA or PE suspected	Thank you for your comment. The committee noted that the recommendation states to think about a low-dose chest CT scan rather than stating to perform this on any child that has not had a CT scan before. Therefore, performing the CT scan would be subject to clinical judgement based on individual circumstances. This has now been explained in the section "Evidence to recommendations" in the full guideline. The committee also discussed your comment on additional indications to perform a chest X-ray but decided not to include these, because the recommendation focuses on exacerbations, therefore these additional indications do not apply.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	14	1.6.10	Induced sputum should also be listed	Thank you for your comment. The recommendation has been amended to mention sputum induction as an example of non-invasive upper airway respiratory secretion sampling, which would be performed before thinking about broncho-alveolar lavage.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	16-17	1.6.26 1.6.30	Why not treat MRSA? Are they referring to chronic infection? In the earlier sections, need to specify MSSA or MRSA or both, its confusing 1.6.30 very loose; what is 'new'? what is "recent"?	Thank you for your comment. The recommendations have been modified and they now state that for people of new evidence of MRSA respiratory infection (with or without pulmonary exacerbation), specialist microbiological advice should be sought on treatment to eradicate it. However antibiotics should not be routinely used to suppress chronic MRSA in people with stable pulmonary disease. If a person with chronic MRSA respiratory infection becomes unwell with a pulmonary exacerbation or shows a decline in pulmonary function, specialist microbiological advice should be sought. The committee discussed your comment about why recommendations first only mention *Staphylococcus aureus*, and then specify MSSA or MRSA. They agreed that recommendations follow the logical treatment pathway for dealing with all *Staphylococcus infection* and only when this is MRSA or MSSA do specific recommendations on these pathogens need to be followed. The committee gave a definition of new *Pseudomonas aeruginosa* infection: recent respiratory secretion sample cultures. The committee agreed that clinical judgement should define recent.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	20	1.6.44	Probably not correct to lump MAI and *abscessus* in the same section any more, management differs. The whole section is poor	Thank you for your comment. The committee decided not to make more detailed recommendations, which would require us to differentiate between different non-tuberculous mycobacteria, because no evidence was found on non-tuberculous mycobacteria. Recommendations on this pathogen have now been amended to state to seek specialist microbiological advice on which antibiotics to use and on the duration of treatment. Moreover, the full guideline mentions that there is existing consensus guidance on the management of non-tuberculous mycobacteria in a publication by Floto et al. (2016) titled "US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis" (http://thorax.bmj.com/content/71/Suppl_1/i1)
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	23	1.7.5	Should this be done annually in a child with 2 mild mutation?	Thank you for your comment. The committee discussed your comment and agreed the test should be done at diagnosis and then repeated if there are symptoms or signs suggesting malabsorption. Therefore the committee removed the recommendation to repeat the test annually. The committee noted that this recommendation does not prevent centres from including this test as part of an annual assessment but it doesn't mandate to do so.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	27	1.7.28	This suggests that there should be no routine BMDs but probably not enough evidence to suggest this practice can be stopped	Thank you for your comment. The Committee agreed it was cost-ineffective and burdensome for people to receive regular scans if their management strategy would not change. The committee's discussion on this area is provided in the full guideline section titled "evidence to recommendations"
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	28		Comment 1: Rather than "serious mental health issue" this should state "significant emotional challenges affecting psychological wellbeing" (e.g. school anxiety; low mood; etc.) Comment 2: Consider (in discussion with the family) Tier 2 referral and/or onward referral to local psychological wellbeing services for further support (e.g. school counsellor, CAMHS). Comment 3: What about referring to NICE guidance for treatment of mental health conditions in children.	Thank you for your comment. Comment 1. The Committee discussed this suggestion but decided to use the term "severe mental health condition" instead, because significant emotional challenges affecting psychological wellbeing could also be dealt with by the specialist clinical psychologist in the CF specialist MDT and would not necessarily prompt referral to a mental health practitioner. Some examples of severe mental health conditions are provided in the full guideline in the section "Evidence to recommendations": psychosis, high level of risk of self-harm or need for psychiatric care. Comment 2. The section "Evidence to recommendations" in the full guideline has also been modified to state that the clinical psychologist should also consider (in discussion with the family) Tier 2 referral or onward referral to local psychological wellbeing services for further support (for example with the school counsellor or CAMHS). Comment 3. The reference to NICE guidelines has now been changed so that no specific

					guidelines are mentioned in the recommendations. However some examples are made in the "Evidence to recommendations" section in the full guideline; these include some NICE guidelines on treatment of mental health conditions in children, for example the guideline on depression in children and young people [CG28].
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	28	3-4	Comment 1: No mention of family and carers of children with cystic fibrosis – this should be stated in this recommendation. Comment 2: as point 23 above	Thank you for your comment. Comment 1: The committee decided to only mention family members and carers in a separate recommendation which is specific to them. Comment 2: The committee discussed your suggestion to use the term "psychological screening" in the key conclusions of the "Evidence to recommendations" section and concluded that the term "assessment" was more appropriate as it was the term used in the recommendations. The recommendations use the term "assessment" rather than "screening" because "assessment" suggests a more individualised and flexible approach. This reflects the fact that no specific recommendations could be made regarding psychological assessment tools as no evidence was found. As explained in the full guideline, the committee highlighted there are no available tools specific to people with cystic fibrosis. For this reason, the committee made a research recommendation about the most effective measure of psychological functioning to use as a screening test for thresholds of concern in people with cystic fibrosis. The committee noted that, although assessment tools are helpful to assess the severity of the psychological or behavioural disorder, in practice psychologists are able to intervene without a formal diagnosis. Therefore, although a screening tool for psychological problems in cystic fibrosis would help, all people and families should be seen regularly by a psychologist who is able to perform assessments using clinical interview as well as screening measures. The committee discussed your suggestions relating to the referral process, however decided not to include this level of detail into the full guideline because discussions with the person or family about referrals, and how to proceed if this is declined by them, would not be specific to cystic fibrosis.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	3		Diagnosis: should stress that diagnosis on clinical grounds alone is much less common, and should be the 3rd not 2nd bullet point. Wording suggests that a gene test is the first test if CF is suspected, which doesn't really tally with the new international guidelines on the diagnosis of CF that still suggests sweat test is the gold standard diagnostic test	Thank you for your comment. The recommendation has now been modified. Diagnosis on clinical manifestations alone is now the last bullet point and we have specified that this is rare. The recommendation only mentions that the blood spot immunoreactive trypsin test would be followed by a sweat and gene test. The Committee decided not to go into more detail in the recommendation itself; however a reference has now been added in the section "Evidence to Recommendations" to the Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK, 2nd Version, by the Royal College of Paediatrics and Child Health.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	4		The list of triggers is incomplete. Should include a family history, male infertility due to azoospermia, hemorrhagic disease of the newborn, portal hypertension of unknown cause, unexpected isolation of a 'CF' organism such as *Ps aer* or *M Abscessus*, nasal polyps should be mentioned specifically	Thank you for your comment. Family history has been added to the recommendation. The recommendation already included obstructive azoospermia. The committee decided not to include haemorrhagic disease of the newborn and portal hypertension of unknown cause because they are very rare. The Committee decided not to include isolation of *P aeruginosa* or *M abscessus* because these pathogens are common in people without cystic fibrosis. Likewise, the Committee decided not to include nasal polyps because are very common in people without cystic fibrosis therefore they would not prompt an assessment for cystic fibrosis on their own. Moreover nasal polyps are rare in children.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	5	3	Replace 'English' with 'in their first language' in these multicultural days and use of an interpreter where necessary	Thank you for your comment. We have changed the wording of the recommendation from information in clear English to information that people with suspected or diagnosed cystic fibrosis and their family members or carers (as appropriate) can understand. The recommendations will not include translation issues because this is not specific to cystic fibrosis. The committee also included a recommendation which directs readers of this guideline to the NICE guideline CG138 "Patient experience in adult NHS services: improving the experience of care for people using adult NHS services". The CG138 guideline recommends: "Establish the most effective way of communicating with each patient and explore ways to improve communication. Examples include using pictures, symbols, large print, Braille, different languages, sign language or communications aids, or involving an interpreter, a patient advocate or family members".
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	6	8-16	The theme of these comments comes across as too adult patient focussed Line 12: At times of change or transition (e.g. starting school) … (then onto adult focussed egs of transition). Line 14: "during pregnancy" – should be "family planning", either patient or parents considering having more children. Missing: considering new treatments, etc. due to deterioration in health (e.g. CFRD) or transplantation.	Thank you for your comment. The following has been added to the recommendation to address your comment: starting or changing school; fertility, including family planning, pregnancy and infertility; waiting for or having organ transplantation. Cystic fibrosis related complications (which would include CFRD) are also included in the recommendation.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	6	9-10	Should instead say "all people with cystic fibrosis and their family members or carers need emotional support, and some may require specialist psychological support".	Thank you for your comment. The committee has discussed your comment and the stem of the recommendation has been amended to state to be aware that people with cystic fibrosis and their family members or carers may need emotional support and some may need specialist psychological support.
Royal Brompton and Harefield	Short	8	24-26	Psychologists do not just work with patients at outpatient clinics and inpatient stays; They may also work with them at separate psychology outpatient appointments and by telephone calls, community visits; school/social care meetings/etc	Thank you for your comment. The recommendation has been modified to state that the specialist clinical psychologists should assess and advise people with cystic fibrosis and their family members or carers (as appropriate) at outpatient clinic visits and (if needed) at other outpatient

Hospitals NHS Foundation Trust					appointments, during inpatient admissions, and at their annual review. The full guideline also mentions some examples of further outpatient appointments: community visits, schools or social care meetings. This section also mention telephone calls, however this was not included in the recommendation not to make it too detailed or over prescriptive, because it would be up to the psychologist and the person they are seeing to agree the setting of their appointment.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	8	7-9	This statement minimises the role of the CF CNS's (ie does not acknowledge their nursing expertise, etc.) This statement also potentially absolves other professionals of their responsibilities in also advocating and coordination communication (although it is acknowledge that the CF CNS is well positioned to take a lead on this)	Thank you for your comment. The recommendation has been amended to include more examples about the clinical role of a specialist nurse.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	8	1.3.13	1.3.13 should also advise on discharge from hospital	Thank you for your comment. The recommendation has been modified and it now states that the specialist pharmacist should advise people on medicines optimisation during inpatient admissions, on discharge from hospital, at outpatient clinic visits and at annual review. The recommendation now also states that they should advise healthcare professionals on all aspects of medicines use and prescribing.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	8-9 (over page)	27 (Page 8) – 7 (Page 9).	Page 9, Line 7: The guideline should state that routine access may need to be from local services as well not just centre care. It may be better for some patients and families, especially for psychiatry.	Thank you for your comment. The committee discussed your suggestion and decided not to make the recommendation too detailed, however it added a sentence in the "Evidence to recommendations" section stating that people with cystic fibrosis would have access to these professionals either through the specialist centre or through referral from their GP.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	9		Should include ENT surgery	Thank you for your comment. ENT surgery has been added to the list.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	9	27-28	Guideline should define "successful (transition)" – or re-word "successful" is subjective. Maybe 'transition from paediatric to adult service is completed'.	Thank you for your comment. This recommendation has been deleted from the guideline and readers are instead directed to NICE guideline NG43 "Transition from children's to adults' services for young people using health or social care services"
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	9	29-30	Missing at end of recommendation: …" to contribute to future service planning and development" (Otherwise asking for feedback is meaningless)	Thank you for your comment. The committee discussed your suggestion and concluded not to make this addition because it is implied. Moreover, the NICE guideline NG43 "Transition from children's to adults' services for young people using health or social care services" goes into more detail about issues relating to feedback and service planning.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	General		1.3.10 No mention of where and when CNS' do their work. No mention as for other professional groups that they work in outpatients/inpatients/community/telecommunications No mention of CNS role as clinicians, during home visits they independently assess and review the patient and family, making clinical decisions as appropriate for their skill set. There role is far more than just a coordinator	Thank you for your comment. The recommendations on the cystic fibrosis specialist nurses have been amended to state that they are in a unique position to coordinate care and communication between other members of the team, and act as advocates for people with cystic fibrosis and their family members or carers. Key clinical roles of cystic fibrosis specialist nurses should include: support during and after diagnosis and when starting treatment; triage; advanced clinical assessment;; coordinating home intravenous antibiotic services including intravenous antibiotics. The committee decided not to specify any settings where cystic fibrosis specialist nurses perform their role because they agreed that their role involves working across all settings.
Royal Brompton and Harefield Hospitals NHS Foundation Trust	Short	General		1.5.2 No mention of the role of CNS nursing assessment at Annual assessment	Thank you for your comment. We have included a nurse and social worker in the assessment bullet point that refers to the annual review.
Royal College of General Practitioners	General	General	General	At present there is only 5 references to GPs and no acknowledgement of their role The Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK Second edition. December 2011 from the Cystic Fibrosis Trust defines some of roles to include The GP is responsible for prescribing much of the routine therapy recommended by the Specialist CF Centre. The Specialist CF Centre must ensure that the GP is adequately informed about the medication recommended particularly when it may be unfamiliar or used out of product license. It is reasonable to expect the GP to provide adequate amounts of medication – a minimum of one	Thank you for your comment. The guideline is mainly concerned with the specialist care and treatment of people with cystic fibrosis. This is usually delivered by specialist MDT teams in specialists CF centres. The majority of the guideline is concerned with the work of those centres and the practitioners who work within them. However the Committee agreed with the RCGP that the guideline should say more about the role of GPs in relation to patients with CF. A new recommendation has therefore been added into the service delivery section of the guideline that sets out some of the key tasks and responsibilities of the GP in relation to supporting people with CF and their families. The recommendation covers prescribing routine CF medicines, annual immunisations, certification of

				month at a time but ideally this would be longer for chronic medications e.g. pancreatic enzymes, vitamins etc. Some local pharmacies and hospitals coordinate an ordering and delivery service. The GP will ensure that patients are fully immunised and arrange for annual influenza immunisation every autumn. The GP will be responsible for non-CF health-related issues. The GP may be asked to be involved with certain referrals, for example fertility and pregnancy issues, and genetic counselling. The GP (as well as hospital consultant) will have responsibility for certification of illness for patients. The GP may be requested to work in partnership with the CF homecare team, particularly in the management of end of life issues. In addition the GP will supporting the other family members and family carers	illnesses, managing health problems not related to CF, working in partnership with CF home care teams, particularly for end of life care and providing care for family members and carers. The committee also agreed that it was important to say more about the GP relationship with the CF specialist pharmacist. The service delivery section of the guideline has therefore been amended to include this and makes reference to the importance of people with CF receiving the medicines they need without interruption.
Royal College of Nursin	Short	7	28	MDT specifics – W.T.E guidance would be beneficial as a minimum for example half a day specialist nurse cover if part of a wider role.	Thank you for your comment. WTEs are provided in appendix K for a range of clinic sizes. However, the Committee did not want to include WTEs in their recommendations to prevent interpretation of a minimum. Instead, the Committee agreed WTEs should depend on the complexity of people with cystic fibrosis at each clinic. The Committee's discussion on this area is provided in the full guideline section titled "Evidence to recommendations".
Royal College of Nursing	Genera l	General	Gene ral	The Royal College of Nursing welcomes proposals to develop this guideline. The RCN invited members who care for people with cystic fibrosis (CF) and other respiratory conditions to review the draft document on its behalf. The comments below reflect the views of our members.	Thank you for your comment.
Royal College of Nursing	Genera l	General	Gene ral	The draft guidelines appear quite comprehensive and set out key outlines for services.	Thank you for your comment.
Royal College of Nursing	Short	10	1.4.1	“almost all males with CF are infertile” – this is too colloquial, the statement should be more specific	Thank you for your comment. This recommendation has been amended to state male infertility caused by obstructive azoospermia (almost all males with cystic fibrosis are infertile). The recommendations in this guideline use plain English in order to be more accessible to people without medical knowledge. There was no evidence on the prevalence of infertility so it was not possible to be more specific. The full guideline explains more in detail the reasoning of the committee behind this recommendation.
Royal College of Nursing	Short	10	1.4.1	Cystic Fibrosis Related Diabetes (CFRD) – affects 1:2 adults (evidence?) maybe this should say “affects up to 1:2 adults”.	Thank you for your comment. The recommendation already stated "affects up to 1 in 2 adults": The full guideline mentions that the UK CF Registry 2015 Annual Data Report showed that the prevalence of people on CFRD treatment among people aged 16 or older was 32%. The Committee agreed that the prevalence of people on CFRD treatment was likely to underestimate the prevalence of people with CFRD because many centres do not know how to accurately test for it. Therefore, based on their clinical experience and expertise, the Committee recommended to be aware that cystic fibrosis-related diabetes is common in people with cystic fibrosis, and it specified that it affects up to 1 in 2 adults.
Royal College of Nursing	Short	11	1.5.2	There is no mention of annual chest x-ray. This is important.	Thank you for your comment. The recommendation states that a comprehensive annual review includes a pulmonary assessment and refers to the recommendations in the section on pulmonary monitoring. The section on pulmonary monitoring recommends to include a chest X-ray at each annual review in relation to pulmonary assessment.
Royal College of Nursing	Short	11	1.5.3	Perhaps local DGH’s need this guidance re regular review, but it is not set in stone. It needs to be patient specific	Thank you for your comment. Based on their clinical experience and expertise, the committee agreed to recommend more frequent routine reviews after diagnosis and in early life. Following those initial years, the person’s condition is likely to become more predictable. To guide the audiences reading the recommendation, the committee gave some examples of review frequency for different age groups, with frequency decreasing with age. The ranges of frequencies provided in the recommendation are not mandatory and should be tailored to the individual with cystic fibrosis. A greater description of the committee’s discussion on this area is provided in the full guideline section titled “evidence to recommendations”
Royal College of Nursing	Short	11	1.5.3	Should read “<u>at least</u> every 3 or 6 months as adults”	Thank you for your comment. The NHS service specifications for cystic fibrosis refer to the CF Trust Standards of Care 2011, which specify that patients should be reviewed with a frequency appropriate to their individual needs. For this reason, the committee provided examples of review frequencies in their recommendation to guide the audience reading the recommendation and allow the frequency to be tailored to the individual. Reviewing each adult every 3 months may not be cost-effective when an adult is stable, but the recommendation does not prevent a review every 3 months in adults if this is considered to be appropriate. A greater description of the committee’s discussion on this area is provided in the full guideline section titled “evidence to recommendations”
Royal College of Nursing	Short	12	1.6.3	Do all centres do routine lung clearance? Not sure about this, especially as not all centres have access to LCI or experience in using. Also, perhaps it should say …. If normal lung function, but child has symptoms e.g. low weight gain, recurring cough, normal cough swabs etc. then consider LCI.	Thank you for your comment. The committee noted that LCI can be a useful tool to assess disease progression as it could provide additional respiratory information to spirometry. However, the committee added that LCI is currently in its infancy in the UK. As a result, the committee made recommendations to consider the use of LCI for those clinics that have access to the equipment and ability to interpret the results. To enable stronger recommendations in the future, a research recommendation to assess if LCI is a useful and cost-effective tool for the routine

					assessment and monitoring of changes in pulmonary status in people with cystic fibrosis was made by the committee. The committee discussed your suggestion to consider LCI only if there are symptoms, however agreed that LCI can also be considered in asymptomatic people with the objective to obtain more information than from spirometry and detect any issues early on.
Royal College of Nursing	Short	13	1.6.5	Definitely appropriate.	Thank you for your comment.
Royal College of Nursing	Short	13	1.6.7	Should 1.6.7 be after 1.6.8?	Thank you for your comment. The committee discussed your comment and agreed not to change the order of these recommendations because the two recommendations are about different population: the first recommendation is about children with cystic fibrosis who have not had a CT scan before, the second recommendation is about people with cystic fibrosis that are receiving or have received treatment for an exacerbation of lung disease.
Royal College of Nursing	Short	16	1.6.22	Are there any alternative medication to be given if the patient is allergic to penicillin?	Thank you for your comment. We have amended the recommendation to state that if children are allergic to penicillins, an alternative oral anti- staphylococcus aureus agent should be considered.
Royal College of Nursing	Short	18	1.6.34	Unclear as to when to use dry powder inhaler (DPI) medication – could this be re-written in a simpler format?	Thank you for your comment. The guideline must adopt existing TA recommendations. For this reason, we cannot reword recommendation 1.6.34 from TA276.
Royal College of Nursing	Short	23	1.7.4	“Short term trial of appetite stimulant” – could this be clarified, how long is “short term”?	Thank you for your comment. We have added up to 3 months as an example in the recommendation.
Royal College of Nursing	Short	25	1.7.17	Should an annual liver ultrasound be recommended? This is not mentioned in this section	Thank you for your comment. One of the recommendations states to perform a liver ultrasound scan if liver function blood tests (performed at the annual review) are abnormal. The section "Evidence to recommendations" in the full guideline explains that the committee noted that if abnormal liver function blood tests are the first indication of liver disease, there are potential cost savings to the NHS if those tests can replace ultrasound scans at the annual review. This saving is particularly the case in adults who are unlikely to develop liver disease without prior suspicion. Following this, the committee agreed that a recommendation in favour of liver function blood tests as the first assessment was warranted. However, the committee agreed that the results from an ultrasound scan could lead to a change in the management strategy when, for example, cirrhosis and portal hypertension (with Doppler) are detected. Given that an ultrasound can add additional information to an abnormal liver function blood test, a recommendation in that subgroup was considered as a cost-effective use of ultrasound scans.
Royal College of Nursing	Short	26	1.7.26	There is no mention of how often CFRD should be tested for in this group of patients.	Thank you for your comment. We could not include the frequency of testing in the recommendation as the review was focussed on the type of monitoring as opposed to the frequency. Moreover, the committee were reluctant to provide a frequency based on consensus, as the frequency should be tailored to the individual with cystic fibrosis according to their need and risk factors. Therefore, the frequency should be determined by clinical decision.
Royal College of Nursing	Short	26	1.7.27	Should “excessive thirst” also be mentioned here?	Thank you for your comment. The committee did not include excessive thirst in their recommendation as this is a feature of Diabetes Mellitus, rather than CFRD and it not often the key indicator someone with CF would present with.
Royal College of Nursing	Short	27	1.7.28	There is no mention of frequency of bone scans or of age of starting bone scans	Thank you for your comment. The committee agreed that the recommendations on BMD should apply to children and adults. The starting age of bone scans is redundant as this depends on the presence of those risk factors highlighted in the recommendation. In the full guideline section titled "evidence to recommendations" it is suggested that scans could be repeated on an annual basis if the BMD SDS score is less than -2.00. However, the committee did not state the frequency of bone scans in their recommendations as this would be individualised to the patient using clinical expertise.
Royal College of Nursing	Short	29	1.8.6	Include age appropriate toys in rooms. Cleaning of toys and rooms between patients. We do not use same toys in same clinics, but the rooms are used again, though cleaned and aired between patients.	Thank you for your comment. The committee agreed that toys and rooms should be cleaned. The committee made a recommendation to prevent cross-infection among people with cystic fibrosis in outpatient and inpatient care using microbiological surveillance and a local infection control strategy. The full guideline clarifies that a local infection control strategy would cover interventions such as cleaning of rooms and equipment, closing the doors of rooms in the hospital or the outpatient clinic and effective ventilation in gyms to remove exposure of airborne cross-infection. The committee noted that cleaning of toys would also fall within the remit of a local infection control strategy, therefore this did not need to be specifically mentioned in the recommendations. The committee also noted there are existing NICE guidelines on preventing and controlling infection. Therefore, the committee incorporated a reference to these guidelines and focussed their recommendations on cross-infection concerns specific to people with cystic fibrosis.
Royal College of Nursing	Short	29	1.8.7	Even during clinic visits, there can be a problem of contact when visiting other hospital’s communal areas such as pharmacy.	Thank you for your comment. The pharmacy has been added to the recommendations on cross-infection. Hospital communal areas are also considered to be covered by referring to diagnostic and treatment facilities.
Royal College of Nursing	Short	3	1.1	It would be beneficial if the National Screening Programme is mentioned as the 1st point.	Thank you for your comment. The recommendation has now been modified and infant screening is mentioned in the first bullet point.
Royal College of Nursing	Short	5	1.2.3	It would be helpful for the information to be provided in a range of languages or patients/carers should have access to translation services.	Thank you for your comment. We have changed the wording of the recommendation from information in clear English to information that people with suspected or diagnosed cystic fibrosis and their family members or carers (as appropriate) can understand. The recommendations will

					not include translation issues because this is not specific to cystic fibrosis. The committee also included a recommendation which directs readers of this guideline to the NICE guideline CG138 "Patient experience in adult NHS services: improving the experience of care for people using adult NHS services". The CG138 guideline recommends: "Establish the most effective way of communicating with each patient and explore ways to improve communication. Examples include using pictures, symbols, large print, Braille, different languages, sign language or communications aids, or involving an interpreter, a patient advocate or family members".
Royal College of Nursing	Short	5	1.2.3	The point ….Implications for “independent living”…. Suggests that people with CF are disabled in some way	Thank you for your comment. Independent living has been changed to living independently. This refers to all stages of life, for example moving out of the family home to go to university, which would present new challenges such as finding privacy to perform daily treatments.
Royal College of Nursing	Short	5	1.2.6	…“Including those aimed at children”… gives the impression that these are groups that meet. We do NOT encourage any adults to meet with their children who have CF. Perhaps this should be revised for clarity, i.e. written or online resources.	Thank you for your comment. We have changed the first bullet to refer to available resources and support, such as local support and advocacy services. The word "groups" has been deleted from the recommendation to avoid giving the impression that these are groups that meet. The section "Evidence to recommendations" also mentions that the committee strongly recommends that support groups do not take place face to face in order to prevent cross-infection which can lead to further complications. Information about online support groups and advocacy services would be beneficial. Facilitating access to parent or carer only face to face social support groups can be considered if there is a demand. But with these, the risk to their children meeting socially must be emphasised.
Royal College of Nursing	Short	6	1.3	Service delivery – there is no mention in this section about patient’s route for admission (e.g. Patients should be able to refer themselves directly to the respiratory ward for admission if required)	Thank you for your comment. The committee discussed your suggestion and concluded to recommend that the specialist cystic fibrosis centre should have a point of contact available at all times (day or night) for urgent enquiries from people with cystic fibrosis and their family members or carers (as appropriate). Following this, the route for admission would be individualised to the patient according to their needs and severity. The committee agreed it would be inappropriate for all patients to be able to refer themselves as this may not take into account the opportunity cost of resources.
Royal College of Nursing	Short	6	1.2.9	This list should also include …“on transplant list”… as another option	Thank you for your comment. We have added waiting for or having organ transplantation to this recommendation.
Royal College of Nursing	Short	7	1.3.5	We feel that it might not be appropriate/reasonable for all CF teams to provide a member on call for 24 hours per day 7 days per week. Might be better to have a number for patients to phone (e.g. CF ward) and the call can then be escalated if appropriate.	Thank you for your comment. The recommendation has been changed to state that the specialist cystic fibrosis centre should have a point of contact available, instead of stating that there should be a member of the multidisciplinary team available. This change was made to allow for variations across the country where this point of contact may be provided by a CF specialist ward or MDT.
Royal College of Nursing	Short	7	1.3.5	The role of CF team is to also promote the empowerment of people, therefore at night, weekends etc. families should also be encouraged to contact their local hospital for urgent enquires, as there are instances where CF teams will be unavailable.	Thank you for your comment. The recommendation has been changed to state that the specialist cystic fibrosis centre should have a point of contact available, instead of stating that there should be a member of the multidisciplinary team available. This change was made to allow for variations across the country where this point of contact may be provided by a CF specialist ward or MDT.
Royal College of Nursing	Short	7	17	It would be prudent to specify what level of contact (day and night) is the minimum as this is currently left to interpretation.	Thank you for your comment. The committee agreed that the recommendation did not need to be more specific about the level of contact people can expect as a minimum because each centre will have their own process for providing this. There should be existing clear processes in place for accessing out of hours at each clinic.
Royal College of Nursing	Short	8	1.3.10	There is no mention of IV antibiotic training. Also very vague description of CF CNS role generally.	Thank you for your comment. The recommendation has been amended to include more examples about the clinical role of a specialist nurse including home IV services and IV access. Also note that IV antibiotic training is included as a recommendation in the section on service configuration which states to make arrangements (including providing equipment and expert support) for people to have intravenous antibiotic therapy at home, when this is appropriate.
Royal College of Nursing	Short	8	1.3.8	Some centres do not have social workers	Thank you for your comment. We have amended the recommendations about the MDT to say that the core MDT should either include or have access to social workers. The Committee agreed a social worker should ideally be included in the core MDT as cystic fibrosis is a lifelong condition that needs continuous assessment and intervention on emerging social problems. This recommendation is also consistent with NHS service specifications for cystic fibrosis.
Royal College of Nursing	Short	9	1.3.16	Should read “Begin to discuss the transition process …”	Thank you for your comment. The recommendation has been amended as you suggested.
Royal College of Nursing	Short	General	General	We only read and commented on the short version of the guideline, so acknowledge that there may be a lot more detail in the full version. However, these short version of the guidelines do seem vague and we presume they are to be used in conjunction with the CF Trust’s consensus documents?	Thank you for your comment. Recommendations are based on the best available evidence and the committee's knowledge and expertise. NICE does not endorse consensus documents without a rigour reviewing process and consultation process. However, any changes to current clinical practice are highlighted in the full guideline with for example, reference to NHS Service Specifications.
Royal College of Nursing	Short	General	General	There is no mention at all of lung transplantation or end of life care which we consider are major components of CF care.	Thank you for your comment. The guideline scope did not include lung transplantation or end of life care as key areas to be covered. However, one theme identified in the review on information and support was end of life care, this is reported in the full guideline. The recommendations on information and support state that when appropriate, people with cystic fibrosis and their family members or carers should be provided with opportunities for discussion with relevant expert professionals on organ transplantation and end of life care. The recommendations on information and support also state to be aware that people with cystic fibrosis and their family members or carers may need emotional support and some may need specialist psychological support, in particular when waiting for or having organ transplantation, and when approaching the end of life.
Royal College	Genera	General	Gene	We agree that the content is appropriate and have no changes to suggest.	Thank you for your comment.

of Paediatrics and Child Health	l		ral		
Royal College of Paediatrics and Child Health	Short	11		For well babies diagnosed by screening who are doing well, monthly appointments up to a year may be unnecessary. At 6 months after diagnosis, this could be reduced to 6-8 weekly.	Thank you for your comment. To guide the audiences reading the recommendation, the committee gave some examples of review frequency for different age groups, with frequency decreasing with age. The ranges of frequencies provided in the recommendation are not mandatory, only examples, and should be tailored to the individual with cystic fibrosis. A greater description of the committee's discussion on this area is provided in the full guideline section titled "evidence to recommendations"
Royal College of Paediatrics and Child Health	Short	12		Most secondary care clinics do not have the facilities to measure lung clearance.	Thank you for your comment. In the full guideline it is noted that LCI is currently in its infancy in the UK, but could provide additional respiratory information to spirometry. As a result the committee made recommendations to consider the use of LCI for those clinics that have access to the equipment and ability to interpret the results. This is a weak recommendation by the use of "consider" and is not mandatory. To enable stronger recommendations in the future, a research recommendation to assess if LCI is a useful and cost-effective tool for the routine assessment and monitoring of changes in pulmonary status in people with cystic fibrosis was prioritised by the committee.
Royal College of Paediatrics and Child Health	Short	12		Testing for mycobacteria is difficult and probably unnecessary in those who do not produce sputum.	Thank you for your comment. The committee discussed your suggestion but decided not to delete non-tuberculous mycobacteria from the recommendation. The committee agreed that microbiological investigations should include non-tuberculous mycobacteria even if testing for this pathogen is more difficult than for other pathogens. The committee noted that if people are unable to produce sputum, cough swabs should be analysed, even if the accuracy of the analysis is lower with cough swabs. The committee noted that currently not all laboratories analyse cough swab for non-tuberculous mycobacteria so the recommendation to include this pathogen among microbiological investigations at annual reviews will be a change to current practice in some centres. However they agreed that it was important to undertake all possible efforts to ensure early diagnosis of non-tuberculous mycobacteria.
Royal College of Paediatrics and Child Health	Short	14		Broncho-alveolar lavage would presumably only be done using bronchoscopy under GA. If this is being done, then a full bronchoscopic examination should also be done. This is not clear.	Thank you for your comment. The committee discussed your comment and agreed that it was correct but decided not mention bronchoscopy because this recommendation is about the indications for broncho-alveolar lavage (BAL). The committee noted that recommendations on how to perform a BAL are beyond the scope of this guideline.
Royal College of Paediatrics and Child Health	Short	15		It is not clear here what is meant by 'mucoactive agents'. Presumably it just refers to saline, DNAse and mannitol. It could be misinterpreted as referring to older discredited mucolytics such as N-acetyl-cysteine. This should be clarified.	Thank you for your comment. The committee discussed your comment and decided to leave the heading as it is because the review looked at more mucoactive agents than the ones included in the recommendations, therefore including all agents in the heading may cause confusion. The mucoactive agents that were considered when drafting recommendations are the ones specified in the protocol for the systematic review on mucoactive agents (please see Appendix D for review protocols). The protocol includes dornase alfa, acetylcysteine, nebulised sodium chloride (saline) hypertonic and isotonic), and mannitol. With regards to acetylcysteine, the full guideline explains why this was not recommended. The committee reviewed the evidence comparing acetylcysteine to placebo. Very low to moderate quality evidence showed no clinically significant differences in FEV1 between acetylcysteine and placebo at 4, 12 and 24 week follow-ups. Likewise, low quality evidence showed no differences in need for additional intravenous antibiotics for pulmonary exacerbation at 24 week follow-up. No clinically significant differences were found in inflammatory markers or quality of life either. The committee also noted that acetylcysteine was not commonly used in clinical practice because of the unpleasant smell and taste. Moreover, acetylcysteine needs to be taken up to 4 times a day, so overall it is less tolerable and more burdensome than other mucoactive agents. Based on this, the committee agreed not to make a recommendation in favour of acetylcysteine.
Royal College of Paediatrics and Child Health	Short	15		There is no indication at what age DNAse should start. Current practice is to start around 5 years of age. It is more effective when the child can manage the nebuliser competently. This should be mentioned.	Thank you for your comment. The review didn't include age, but the committee agreed that if a patient had clinical evidence of lung disease, rhDNase would be started regardless of age.
Royal College of Paediatrics and Child Health	Short	15		There should perhaps be a reference to the practice of using hypertonic saline only during exacerbations, or when there is a need to induce sputum for microbiological diagnosis.	Thank you for your comment. The committee decided not to add a reference to exacerbations or to the need to induce sputum. No evidence was reviewed on hypertonic sodium chloride when there is a need to induce sputum. One study (Dentice 2016) compared 7% sodium chloride to 0.12% sodium chloride in a population admitted for management of a pulmonary exacerbation. One other study (Wilmott 1996) compared rhDNase to placebo in a population admitted to hospital for at least 1 night for treatment of a chest exacerbation. However none of the included studies compared rhDNase and hypertonic sodium chloride in a population with a pulmonary exacerbation. Therefore, the committee did not make specific recommendations on a first choice mucoactive agent in people with pulmonary exacerbations. The committee reviewed the available evidence comparing nebulised rhDNase to hypertonic sodium chloride, which was not specific to exacerbations and showed significant differences in FEV1 in favour of dornase alfa at 3 month follow-up but not at 3

					week follow-up. The evidence was low or very low quality. Due to the limited evidence, the committee relied on their expertise and experience to guide their decision as to whether rhDNase or hypertonic sodium chloride should be the first-line treatment. On balance, they agreed that rhDNase was more effective and tolerable, and insufficient evidence was presented to change currently accepted practice. Therefore, the committee recommended rhDNase as first choice treatment and hypertonic sodium chloride as second choice treatment. Mannitol was recommended as an option in adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and whose lung function is rapidly declining (forced expiratory volume in 1 second [FEV1] decline greater than 2% annually) and for whom other osmotic agents are not considered appropriate. These recommendations were in agreement with the NICE TA266. The committee also recommended to consider mannitol in children and young people only if there was inadequate response or intolerability to rhDNase and hypertonic sodium chloride. The committee noted that the evidence showed no benefit nor harm of mannitol in children and young people. The committee noted that mannitol is rarely used in clinical practice in this age subgroup. They were aware of issues of poor tolerability and difficulties with the inhaler device in children and young people.
Royal College of Paediatrics and Child Health	Short	16		There is no mention here of using long-term inhaled tobramycin to prevent Staph. aureus, with or without flucloxacillin, which is common practice.	Thank you for your comment. The committee discussed your comment and decided not to recommend inhaled tobramycin as antibiotic prophylaxis to prevent pulmonary bacterial infection with *S aureus* because inhaled tobramycin was not included in the review protocol on the effectiveness of long-term antimicrobial prophylaxis to prevent pulmonary bacterial colonisation with *S aureus* in people with CF (Appendix D), therefore the evidence on this was not reviewed.
Royal College of Paediatrics and Child Health	Short	18		We are disturbed by the inclusion in a NICE guideline of a discounted access scheme from a manufacturer. These schemes come and go and costs change. This should not be enshrined by NICE, as it could lead to accusations of commercial bias in the production of the guideline. DPI products should be recommended or not recommended according to the evidence of their effectiveness. DPIs could be recommended where patients' adherence to nebuliser treatments is a problem.	Thank you for your comment. Significant changes to acquisition costs are highlighted during NICE surveillance and could warrant an update to the guideline in those areas. Recommendations on tobramycin DPI and colistimethate sodium DPI are adopted from NICE TA276 that used the Appraisal Committee's knowledge and expertise to interpret the clinical and economic evidence to recommend a cost-effective use of NHS resources. DPI products are recommended in this review when nebulised products are contraindicated, not tolerated or not produced an adequate response.
Royal College of Paediatrics and Child Health	Short	21		The guidance about NTM management appears to be less aggressive than other published guidance. Other guidance suggests full treatment if cultures are positive even if the patient is well.	Thank you for your comment. Recommendations are based on the best available evidence and the committee's knowledge and expertise. The strength of NICE recommendations reflects the quality of the evidence that supports them. Unfortunately no relevant evidence was identified to justify stronger recommendations in this area.
Royal College of Paediatrics and Child Health	Short	25		Abdominal surgery for any reason should only be carried out in a specialist centre, with the involvement of the CF team.	Thank you for your comment. The committee agreed that the recommendation does not need to specify that surgery should be carried out in a specialist centre, as all CF-related care should be managed by the CF centre.
Royal College of Paediatrics and Child Health	Short	25		Some definition of abnormal LFTs is needed. Liver enzyme levels often fluctuate in the absence of significant liver involvement. If the threshold is too low, UDCA may get prescribed unnecessarily. I suggest: 'if liver enzyme levels (ALP, ALT, GGT) are above twice the upper limit of normal on at least two occasions, at least one month apart'.	Thank you for your comment. The committee discussed your suggestion and decided not to include a definition of abnormal liver function blood tests to allow for clinical judgement to decide what tests are abnormal.
Royal College of Paediatrics and Child Health	Short	25		Liver disease can exist even in the presence of relatively normal LFTs. Routine USS can pick up liver problems missed by LFT screening. We suggest routine liver USS at annual review every 2 years, during the high-risk age for new-onset LD i.e. 10-16 years. Repeat annually if LFTs abnormal or any abnormality on scan. If scan normal at age 16, no need to repeat.	Thank you for your comment. The committee discussed your comment and decided not to recommend routine ultrasound screening for liver disease because the evidence did not support this. The recommendations state to perform a clinical assessment and liver function blood tests at the annual review. The committee agreed that decisions on the tests to be included in the clinical assessment should be made at individual centres using clinical judgement. This means that individual centres would not be prevented from including an ultrasound scan at every annual review, or every two years. The committee noted that it is currently common practice to perform blood test investigations to look for evidence of liver disease. The committee recognised that ultrasound can detect evidence of liver disease, for example changes in liver echogenicity as well as advanced changes suggestive of portal hypertension. It can also detect the presence of gallstones which sometimes occur in cystic fibrosis. Ultrasound scanning is commonly used to monitor cystic fibrosis-related liver disease. The committee agreed that this may not be necessary if there was no evidence of liver disease, but a liver ultrasound scan should be performed if the blood liver function tests were abnormal. This has now been clarified in the "Evidence to recommendations" section in the full guideline.
Royal College of Paediatrics and Child Health	Short	26		Last bullet point unclear, needs re-writing.	Thank you for your comment. If you are referring to the bullet on "excessive tiredness" this is increased tiredness compared to the normal level of tiredness for that individual, so would depend on their history. The committee did not want to quantify "excessive tiredness" as this is relative to the individual.
Royal College of Paediatrics and Child Health	Short	28		Psychologist should not only be available but should actively see families at every visit.	Thank you for your comment. The Committee agreed that it was better to have a less prescriptive recommendation which would allow to determine frequency of visits based on individual needs. The section "Evidence to recommendations" relating to psychological assessment mentions that the frequency of visits to the psychologist should be based on individual needs as it would be

					cost-ineffective to monitor each individual using the same schedule, when the opportunity cost of the psychologist's time is high.
Royal College of Paediatrics and Child Health	Short	28		Psychologist should also consider the needs of non-CF siblings, as this is often neglected by professionals	The Committee agreed that the psychologist should also assess the needs of non-CF siblings. These are included under "family members" in the recommendations. The recommendation has now been amended to specify that the specialist clinical psychologist should assess any cystic-fibrosis-related needs of family members or carers, support their psychological wellbeing and refer them to mental health practitioners as needed. The full guideline explains that the clinical psychologist should assess their needs in relation to the impact of cystic fibrosis. If psychological needs were more of an individual nature rather than related to cystic fibrosis, the clinical psychologist would refer them to the GP who would then provide onward referral to a mental health practitioner.
Royal College of Paediatrics and Child Health	Short	29		Could include pharmacy	Thank you for your comment. The recommendation has been changed to refer to attendance at diagnostic, treatment and pharmacy facilities to address your comment.
Royal College of Paediatrics and Child Health	Short	3	1.1, line numb er 10	Diagnosis guidance contains very little on neonatal screening, which is now by far the most common means of diagnosis. This can be a complex area, particularly when IRT is high and only one mutation identified initially. This may be too large an area to include in this guideline, in which case reference should be made to guidance from PHE on https://www.gov.uk/government/collections/newborn-blood-spot-screening-programme-supporting-publications#cystic-fibrosis-(cf)	Thank you for your comment. A reference to this guideline has been added in the section "Evidence to recommendations", in the sub-section "Other considerations".
Royal College of Paediatrics and Child Health	Short	34		A screening tool for psychological problems would help, but as stated above, all patients and families should be seen regularly by a psychologist anyway. There may be little direct evidence of benefit for routine psychological support in CF specifically, but it is reasonable to extrapolate form other chronic conditions, e.g. diabetes, where it has been shown to improve outcomes. Particularly in adolescence, having a long-term life-threatening illness is always a psychological problem, even if not overt. Early psychological support should reduce poor adherence in adolescence, which is a major determinant of reduced survival. NICE should emphasise this.	Thank you for your comment. The justification for the research recommendation justifies why it is important to research tests for thresholds of concern. The section on evidence to recommendations emphasises the importance of the clinical psychologist in cystic fibrosis care and has now been modified to mention that although assessment tools are helpful to assess the severity of the psychological or behavioural disorder, in practice psychologists are able to intervene without a formal diagnosis. Therefore, although a case finding tool for psychological problems in cystic fibrosis would help, all people and families should be seen regularly by a psychologist. The Committee noted that routine psychological support is important to improve outcomes in a chronic and life-threatening illness. Early psychological support can improve adherence to long-term medications in adolescence, which is a major determinant of life expectancy.
Royal College of Paediatrics and Child Health	Short	4		'Refer to specialist CF centre if gene testing reveals 1 or 2 CF mutations' This would apply to 1 in 25 of the UK population when tested. This is too low a threshold for specialist referral. I assume it refers to neonatal screening. If only 1 mutation and repeat IRT is normal, and baby has no FH and no symptoms, in my view specialist referral is unnecessary. Parents can be carefully counselled and the baby followed in secondary care, while awaiting results of genetic tests for rare mutations. If none found and baby remains well, can be discharged after a few months. Unnecessary specialist referral wastes resources, induces parental anxiety and suggests abnormality in what is probably a normal baby.	Thank you for your comment. No change has been made to the recommendation because this recommendation refers to people with suspected cystic fibrosis based on symptoms listed in the previous recommendation. Therefore, this recommendation does not refer to neonatal screening in the general population. The Committee agreed that the number of referrals would be too high if this recommendation applied to the general population. However, given that it only applies to people with suspected cystic fibrosis, the number of referrals would be manageable.
Royal College of Paediatrics and Child Health	Short	7		We agree with the emphasis on shared care for children. This model is widely adopted and works well. However twice yearly reviews by tertiary specialist team should not be mandatory. For children who are doing very well with no problems, annual review may be sufficient. Tertiary team should be kept informed about every secondary care clinic consultation.	Thank you for your comment. The committee agreed that all people with cystic fibrosis should have an annual assessment and at least one other review per year with the specialist centre multidisciplinary team in order to identify early on any clinical deterioration. This minimum frequency is consistent with the CF Trust Standards of Care 2011, which are referred to in the NHS service specification for cystic fibrosis.
Royal College of Paediatrics and Child Health	Short	8		Specialist physiotherapists should also be expected to undertake spirometry, especially where no respiratory lab facilities are available.	Thank you for your comment. The committee agreed that spirometry should not be added to the list as this is not an expected role of a physiotherapist. Instead, this is the role of any healthcare professional who is sufficiently trained. However, this recommendation does not exclude physiotherapists from being trained to perform spirometry.
Royal College of Paediatrics and Child Health	Short	8		We would like to see a recommendation that a psychologist sees the patient/family at *every* clinic visit, not just annual review, as a team member with equal status to other professionals.	Thank you for your comment. The recommendation has been modified to state that the specialist clinical psychologists should assess and advise people with cystic fibrosis and their family members or carers (as appropriate) at outpatient clinic visits and (if needed) at other outpatient appointments, during inpatient admissions, and at their annual review. The full guideline explains that the Committee agreed that the frequency of visits to the psychologist should be based on individual needs as it would be cost-ineffective to monitor each individual using the same schedule, when the opportunity cost of the psychologist's time is high.
Royal College of Paediatrics and Child Health	Short	General	Gene ral	Generally this is a welcome document which is largely in line with current UK practice. It replicates much of the guidance issued by the CF Trust and others.	Thank you for your comment.
Royal College of Physicians	Genera l	General		The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the British Thoracic Society.	Thank you for your comment.
Teva UK Limited	Full	General		We agree with the recommendations as detailed by NICE in the consultation document.	Thank you for your comment.

The Royal College of Radiologists (RCR) and the British Society of Thoracic Imaging (BSTI)	Short	13	1.6.7	Should be added as mention: In patients with cystic fibrosis specific low dose CT protocol should be considered as these patients may require many CT scans during their life with associated radiation dose. Moreover, with modern CT techniques it is possible to get high quality long CT at a much lower dose than previously. Many patients with CF are thin and therefore low dose CT is particularly appropriate.	Thank you for your comment. We have amended the recommendation to state that the chest CT scan should be low-dose. Moreover, in the section "Evidence to recommendations" we have used the rationale provided in your comment to explain why the CT scan should be low-dose.
The Royal College of Radiologists (RCR) and the British Society of Thoracic Imaging (BSTI)	Short	22	1.6.52	Consideration on imaging (CXR and/or CT) could also be added to this section on unidentified infective exacerbation.	Thank you for your comment. The committee discussed your suggestion and decided not to include radiological investigations in this recommendation because this recommendation is about treatment rather than about investigations. Please refer to the section on pulmonary monitoring for recommendations about investigations and use of imaging techniques.
The Royal College of Radiologists (RCR) and the British Society of Thoracic Imaging (BSTI)	Short	24	1.7.10	Consider changing the wording of 1.7.10 about acute onset periumbilical abdominal pain. Perhaps “initially by ultrasound and followed by MRI or CT if the cause is not confirmed via ultrasound and clinical concern persists”…abdominal CT in young and very thin CF patients is a big source of ionising radiation dose and may not be rewarding. This is one area where MRI is already established enough to be clinically useful.	Thank you for your comment. The committee discussed your suggestion and noted that no evidence was reviewed on diagnosis of DIOS, therefore only consensus recommendations were made. The committee did not feel confident to make recommendations on using one imaging technique before the other based on consensus only. Therefore they decided that the choice of imaging technique should be left to clinical judgement. The committee did not refer to MRI specifically in the recommendations, but stated to consider further imaging, for example.., so that the recommendation also indirectly refers to MRI and not only to the abdominal ultrasound scan or to the abdominal CT scan. The committee decided to leave the specific examples referring to abdominal ultrasound scan and abdominal CT scan in the recommendation because these are more commonly performed. The committee also noted that the CT scan is less costly and less time consuming than an MRI scan.
The Royal College of Radiologists (RCR) and the British Society of Thoracic Imaging (BSTI)	Short	25	1.7.18	Consider mention “ultrasound liver elastography” in the liver disease section	Thank you for your comment. The section titled "evidence to recommendations" in the full guideline provides the committee's discussion on ultrasound liver elastography. The committee agreed there was little evidence to support the use of ultrasound liver elastography (FibroScan®) for early stage detection of liver disease, and agreed that because treatment with ursodeoxycholic acid would have already been initiated, the value of adding this test to a diagnostic regimen was diminished.
The Royal College of Radiologists (RCR) and the British Society of Thoracic Imaging (BSTI)	Short	3	1.1.1	Maybe add that “Occasionally Chest CT may have been performed in a symptomatic patient, with no previous diagnosis of Cystic Fibrosis(CF), confirming the presence of bronchiectasis- features prompting further clinical tests (sweat test etc.) to confirm the diagnosis of CF.”	Thank you for your comment. This has not been added to this recommendation because it is included in the following recommendation, which lists the symptoms that would prompt an assessment for cystic fibrosis.
The Royal College of Radiologists (RCR) and the British Society of Thoracic Imaging (BSTI)	Short	8-9	1.3.15	Need to add “diagnostic and interventional radiology”. And add that “There should be specialist access to thoracic radiology within the MDT team (e.g requires familiarity with CT appearances of atypical mycobacterial disease, ABPA etc. as mentioned in the document)”	Thank you for your comment. The committee agreed not to add a “diagnostic radiologist” because the diagnostic radiologist wouldn’t need to be specialist in cystic fibrosis, whereas the interventional radiologist would.
UK Psychosocial Professionals in CF (UKPPCF)	Appendix N	Title page		Refers to metal analysis instead of meta analysis	Thank you for your comment. This has been amended.
UK Psychosocial Professionals in CF (UKPPCF)	Full	130	2	Please consider including need for social work support and social work assessment. CF Specialist social workers supports the child and family’s long term adjustment to treatment by supporting their educational needs, providing advice and advocacy support for their welfare entitlements, respite care needs and emerging quality of life issues across the life span.	Thank you for your comment. The recommendations have been amended to include examples about the role of the CF social worker. These include adjusting to long term treatment but also support and advice relating to education or employment. Moreover, in the section "Evidence to Recommendations" related to the information and support review, a sentence has been added to specify that additional support may be needed during times of change, such as starting or changing school, moving from education to work, changing to independent living. The committee noted that social work support is also important at these times and especially liaison with local Social Care services as appropriate.

UK Psychosocial Professionals in CF (UKPPCF)	Full	170-174	38	We are concerned that the recommendation for patients to have annual review did not include their social care needs given that the condition is progressive and peoples' social care needs are likely to change	Thank you for your comment. We have included a nurse and social worker in the assessment bullet point that refers to the annual review.
UK Psychosocial Professionals in CF (UKPPCF)	Full	171	9	We are concerned that this recommendation may imply that the social care needs of people with CF are not as important as their health needs. The document acknowledged that cystic fibrosis is associated with poor quality of life and clinical outcomes. The role of all the other MDT members is stated in the document and that of social work is not. Instead some of the responsibilities of social workers are assigned to the specialist nurses. Please consider including assessment by a specialist social worker. The CF social workers currently employed by NHS Trusts are integrated within the CF multidisciplinary team and are part of annual reviews.	Thank you for your comment. The recommendations have been amended to acknowledge that not every specialist CF MDT team will have access to dedicated social worker. Where social workers are available they are members of the core MDT team. We have also added a recommendation which includes some examples about their role on the MDT. We have also included a nurse and social worker in the assessment bullet that refers to the annual review.
UK Psychosocial Professionals in CF (UKPPCF)	Full	174	40	Please consider including the role as a specialist social worker as they work within the CF multidisciplinary team	Thank you for your comment. A recommendation has been added to the section on the multidisciplinary team to include some examples about the role of the social worker as part of the MDT. These include adjusting to long term treatment but also support and advice relating to education or employment.
UK Psychosocial Professionals in CF (UKPPCF)	Full	177	19	Currently reads "when needed at outpatient and inpatient clinics". Inpatient care is not in clinic so would better read "when needed at outpatient clinics and during inpatient admissions"	Thank you for your comment. "inpatient admissions" has now replaced "inpatient clinics". Moreover, "and (if needed) at other outpatient appointments" has been added after "at outpatient clinic visits" in this recommendation, because some meetings with the psychologist might take place in settings such as community visits, school or social care meetings.
UK Psychosocial Professionals in CF (UKPPCF)	Full	177	19	Please include a separate line stating that the specialist social worker should assess and intervene with people with cystic fibrosis at their annual review, and when needed at outpatient clinics and during inpatient admissions.	Thank you for your comment. A recommendation has been added to the section on the multidisciplinary team to include some examples aboutthe role of the social worker. This recommendation does not specify the setting where this would take place because social workers are not employed by the NHS and therefore are outside the scope of this guideline, and the recommendation could not be too prescriptive. Moreover, the recommendation on the annual review has been modified to include assessment by the social worker.
UK Psychosocial Professionals in CF (UKPPCF)	Full	19	6	We would like it to include - Recognising social, psychological and behavioural problems. NHS Trusts across UK and Ireland have recognised the need for a Specialist CF Social worker to systematically assess and intervene on the emerging social problems due to CF being a lifelong condition.	Thank you for your comment. The recommendations have been amended to include examples about the role of the CF social worker. These include adjusting to long term treatment but also support and advice relating to education or employment.
UK Psychosocial Professionals in CF (UKPPCF)	Full	19	31	Please consider including - Transition from children's to adults' services for young people using health or social care services NICE guideline, 2016	Thank you for your comment. We have directed readers to NG43 Transition from children's to adults' services for young people using health or social care services.
UK Psychosocial Professionals in CF (UKPPCF)	Full	655	21	Typo – this should read the	Thank you for your comment. Unfortunately we cannot identify the typo you are referring to.
UK Psychosocial Professionals in CF (UKPPCF)	Full	667	11-12	Currently reads "If a severe problem is identified as part of the annual review the person should be referred to a mental health practitioner". We feel this advice is ambiguous. Clinical Psychologists are able to work with severe problems in people with CF eg severe anxiety, severe depression, referral outside the team may not therefore be needed in these cases. Referral outside the CF team should be made when there is a severe mental health condition eg psychosis, high level of risk or need for psychiatric care. This would normally involve a "stepping up" of care into specialist mental health services, not to any mental health practitioner. Significant risk would be managed within local mental health services rather than in the CF team.	Thank you for your comment. The section "Evidence to recommendations" in the full guideline has now been modified to include specific examples of a severe mental health condition that would prompt referral to a mental health team. The same section currently states that if a severe mental health condition is identified as part of the annual screening such as psychosis, high level of risk of self-harm or need for psychiatric care, the person should be referred to a mental health team. This would normally involve a "stepping up" of care into specialist mental health services.
UK	Full	669	27-28	As in comment 14.	Thank you for your comment. We understand the request is to change a mental health

Psychosocial Professionals in CF (UKPPCF)					practitioner to "the" mental health practitioner. The committee have not discussed having access to CF specific psychiatrists or psychiatric nurse staff. This recommendation is aimed at when someone is identified as having a severe mental health condition such as psychosis, high level of risk of self-harm or need for psychiatric care, which is not specifically related to their CF or may require pharmacological input or input from community or inpatient psychiatric services. To state "the" mental health practitioner would indicate this should be someone within the CF MDT which may not be the case. The section “Evidence to recommendations” has been amended to specify that the person should be referred to a mental health practitioner who would be part of the local mental health team.
UK Psychosocial Professionals in CF (UKPPCF)	Full	669	43-44	As in comment 14	Thank you for your comment. We understand the request is to change a mental health practitioner to "the" mental health practitioner. The committee have not discussed having access to CF specific psychiatrists or psychiatric nurse staff. This recommendation is aimed at when someone is identified as having a severe mental health condition such as psychosis, high level of risk of self-harm or need for psychiatric care, which is not specifically related to their CF or may require pharmacological input or input from community or inpatient psychiatric services. To state "the" mental health practitioner would indicate this should be someone within the CF MDT which may not be the case. The section “Evidence to recommendations” has been amended to specify that the person should be referred to a mental health practitioner who would be part of the local mental health team.
UK Psychosocial Professionals in CF (UKPPCF)	Full	669	40	We were unclear what “psychosocial indicators” referred to or included.	Thank you for your comment. This term has now been modified to indicators of emerging psychosocial problems. The "Evidence to recommendations" section also gives some examples of said indicators: poor school attendance, family break up, anxious thoughts, low mood, missing treatments, financial or home management difficulties, safeguarding concerns, employment support needs or criminality.
UK Psychosocial Professionals in CF (UKPPCF)	Full	669	42	“Serious mental health issue” is unclear. Severe mental health problem/condition may be more appropriate term here.	Thank you for your comment. This term has now been modified to severe mental health condition.
UK Psychosocial Professionals in CF (UKPPCF)	Full	670	4-5	Sentence does not seem clear. Perhaps should read “to use as a screening test”	Thank you for your comment. The research question has been amended to what is the most effective measure of psychological functioning to use as test for thresholds of concern in people with cystic fibrosis. .
UK Psychosocial Professionals in CF (UKPPCF)	Short	11	16	Social worker assessment should be included here.	Thank you for your comment. We have included a nurse and social worker in the assessment bullet point that refers to the annual review.
UK Psychosocial Professionals in CF (UKPPCF)	Short	6	16	Useful to add “when experiencing major changes in health or serious health events”	Thank you for your comment. The committee discussed this suggestion and decided that this addition was not needed because the recommendation was more specific and focused on specific times when additional support may be needed due to major changes in health. They specifically mentioned pregnancy, cystic fibrosis related complications, transplantation, approaching end of life.
UK Psychosocial Professionals in CF (UKPPCF)	Short	8	26	Useful to add “ The specialist clinical psychologists should also offer advice/consultation to the CF team on psychological care”	Thank you for your comment. The committee discussed your suggestion and decided not to specify this because it is expected of all members of a multidisciplinary team that they would support each other through advice and consultation in relation to their respective areas of expertise.
UK Psychosocial Professionals in CF (UKPPCF)	Short	8	26	Social work roles are omitted here although are listed in essential MDT.	Thank you for your comment. A recommendation has been added to the section on the multidisciplinary team to include some examples about the role of the social worker on the MDT.
University Hospital Southampton	Full	177	15	The specialist pharmacist should be available to advise on medicines and their optimisation during in-patient stay as well as at AR and outpatients (particularly when in-patient ward covered by a non-specialist pharmacist).	Thank you for your comment. The recommendation has been modified and it now states that the specialist pharmacist should advise people on medicines optimisation during inpatient admissions, on discharge from hospital, at outpatient clinic visits and at annual review. The recommendation now also states that they should advise healthcare professionals on all aspects of medicines use and prescribing.
University Hospital Southampton	Full	260	22	There is internal inconsistency with the recommended review period. Here it recommends at least every three months, whereas elsewhere eg page 171 line 17 it says every 3 or 6 months.	Thank you for your comment. The committee recommended routine reviews at least every 3 months for adults with cystic fibrosis with clinical evidence of lung disease. A separate recommendation relating to the general population of adults with cystic fibrosis mentions an example of frequency of 3 to 6 months. As explained in the section "Evidence to

					recommendations", frequency of routine reviews would vary based on individual needs, therefore "3 to 6 months" is given as an example rather than as a standard to be followed for all adults. Given that the recommendation states “For example”, it does not prevent more frequent or less frequent reviews and does not contradict any other routine review timetables in the guideline.
University Hospital Southampton	Full	260	26 and 41	Although ‘clinical history’ may be considered to include medication review, CF is so complex, with so many long term medications, and with adherence being so important, suggest should include explicit recommendation to review medication and adherence at each routine clinic appointment and annual review	Thank you for your comment. The recommendations on routine reviews and on annual reviews relating to pulmonary assessments have now been amended to specify that each review should include a review of medicines adherence. Moreover, a separate recommendation on annual review (not specific to pulmonary assessment) mentions that the annual review should include assessment by a pharmacist. The recommendation on the role of specialist pharmacists mentions that they should advise on medicines optimisation at outpatient clinic visits, during inpatient admissions, on discharge from hospital and at annual review.
University Hospital Southampton	Full	262	2	Why is this recommendation only for children and young people, not all adults?	Thank you for your comment. The recommendation has now been amended to state "people" rather than "children and young people".
University Hospital Southampton	Full	459	25	If making recommendations, surely discussion about abscessus being at least a potential contra-indication to transplant needs to be mentioned as influencing treatment decisions? I.e. if abscessus (with sub-speciation differences noted), and PWCF could be a candidate for transplant, then needs eradication. These guidelines seem insufficiently detailed to be adequate to guide these crucial decisions.	Thank you for your comment. The committee decided not to make more detailed recommendations because no evidence was found on non-tuberculous mycobacteria. However recommendations on this pathogen have now been amended to state to seek specialist microbiological advice on which antibiotics to use and on the duration of treatment. Moreover, the section "Evidence to recommendations" in the full guideline has been amended to state that there is existing consensus guidance on the management of non-tuberculous mycobacteria in an article by Floto et al. (2016) titled “US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis” (http://thorax.bmj.com/content/71/Suppl_1/i1)
University Hospital Southampton	Full	460	24	‘Raised aspergillus serology’ is not a sufficiently specific statement to justify treatment for ABPA. A raised total IgE is required greater than 500 or 1000iu depending on the guidelines you choose. Aspergillus specific IgG may be raised but is not diagnostic of ABPA. This raises the issue of fungal bronchitis, which is not recognised by all clinicians, but which may warrant a trail of treatment. These recommendations do not seem detailed enough to be useful in this complex area.	Thank you for your comment. The recommendation has been amended. It now specifies that elevated aspergillus serology refers to aspergillus-specific IgG and/or IgE. The recommendation now also refers to other aspergillus airway disease in addition to ABPA. The committee discussed your comment about the recommendations not being detailed enough but decided not to provide more detail because very limited evidence was identified on infection with aspergillus.
University Hospital Southampton	Full	530	21 and 45	Despite low quality evidence to support the use of oral supplements, enteral feeding and appetite stimulants (likely due to small numbers) we do find that in clinical practice they are extremely successful for some patients in clinical practice. We wanted to reassure the committee that we don’t want to add to unnecessary treatment burden in this group of patients and are under constant pressure to justify the use of these in the community due to high costs. We therefore closely monitor use of these products and discontinue if no positive outcome.	Thank you for your comment. A sentence has been added to the full guideline specifying that these treatments should be closely monitored and discontinued if there are no positive outcomes. Please note that the quality of the evidence ranged from high to very low. The section "Quality of evidence" in the full guideline, and the GRADE tables in appendix J, provide more information on the quality of the evidence.
University Hospital Southampton	Full	594	19	We would request that specific mention of the latest type of CGM monitoring devices, ‘intermittently viewed’ CGM (such as eg Freestyle Libre) were specifically mentioned. We would also like to express concern over any guideline that recommends the diagnosis of CFRD based on CGMS, for which no definition of DM exists.	Thank you for your comment. The NICE manual states that any references to products should be made in general terms to avoid giving the impression that NICE endorses a particular brand. However, the cost of some CGM systems such as Dexcom G4, Abbott Freestyle and Medtronic RT Guardian are provided in appendix k. Given the uncertainty on CFRD thresholds, the committee did not make a recommendation regarding a diagnostic threshold. Following this, the committee made a recommendation to diagnose CFRD using dynamic testing to enable the clinic to enable them to use the test they have expertise in.
University Hospital Southampton	Full	607	34-43	We keep a bone database which includes all patients who have had a bone scan revealing low bone mineral density (osteopenia/osteoporosis as per WHO Guidelines). A review of the database revealed 50 patients who have a low bone mineral density but do not meet the “high risk” criteria set out in the proposed NICE Guidelines (frequent or long-term oral corticosteroid use, frequent intravenous antibiotic use, severe lung disease, undernutrition, previous low-impact fractures , previous transplants, post menopause). This means that if we were to adhere to the NICE guidelines we would have missed the presence of low bone mineral density in 18.5% of our total adult patient group (*n*=270). We run an innovative joint CF/rheumatology service with the help of Professor Nigel Arden from University of Oxford and MRC. We would be happy to share our experience with the committee.	Thank you for your comment and for sharing your results: the committee noted that these seem to fall within a normal distribution. The CF trust advises to scan people with CF over the age of 10 every 1 to 3 years, but that advice is not evidence based. Instead, the committee agreed that it would only be cost-effective to scan people who would benefit from a change in their treatment strategy. Given that most people with CF receive vitamin D supplementation, it is unlikely their treatment would be escalated. In other words, when scanning is limited to the high risk groups, management won't change where routine scanning has stopped. Overall, this is a weak recommendation by the use of "consider" and will not prevent clinicians from scanning other people with cystic fibrosis should they wish to do so.
University Hospital Southampton	Full	708	34	There is no mention of the need for cross infection surveillance using strain typing (for pseudomonas, cepacia and MRSA) or whole genome sequencing (for M abscessus) on a routine basis eg once a year. Without this, how can you tell if CI is a problem or not? This is in the National Service Specification	Thank you for your comment. The committee recommended to use microbiological surveillance but did not specify the type of microbiological surveillance in their recommendations because no evidence was reviewed on how to perform microbiological surveillance. The committee agreed that their knowledge and expertise alone was not enough to warrant a change from current clinical practice and any additional use of resources and concluded that arrangements relating to microbiological surveillance should depend on the expertise and prevalence of pathogens within each clinic.
University Hospital Southampton	Full	709	6	The word “managed” is too vague to be useful as it could be interpreted in many different ways. Mixing for PWCF is clearly a bad idea (with good evidence) so change this word to ‘avoided’	Thank you for your comment. This recommendation has been amended to state that people should be separated individually during clinics, including by organising the use of communal areas and attendance at diagnostic, treatment and pharmacy facilities.
Vertex Pharmaceutica				The scoping statement of these guidelines states;	Thank you for your comment. CFTR modulators were not included in the scope as current clinical practice in this area was considered to be consistent and effective, relative to the other

ls (Europe) Ltd	Full and Short Full	General	General 3.4.2	This guideline covers the diagnosis and management of cystic fibrosis. It specifies how to monitor the condition and how to manage the symptoms, to improve the quality of life for people with cystic fibrosis. There are also recommendations about treating the most common infections in people with cystic fibrosis, preventing cross infection, service organisation, and information and support. There is no reference made in the draft relating to; i) the efficacy and clinical benefits of CFTR modulators, specifically Kalydeco (ivacaftor) ii)the current clinical practise which includes use of CFTR modulators, specifically Kalydeco (ivacaftor) nor the commissioning policies which are currently in place for Kalydeco (ivacaftor) We contend that by omitting Kalydeco (ivacaftor) and CFTR modulators from these formal guidelines creates significant clinician and patient confusion which is at odds with the scoping statement of these guidelines. In July 2015 NHS England published the clinical commissioning policy making ivacaftor routinely available in CF patients aged from 6 years (see below) https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/a01pc-ivacftr-cystic-fibrosis.pdf In December 2016 NHS England published the clinical commissioning policy for ivacaftor granules for CF patients aged between 2 – 5 years (see below) https://www.england.nhs.uk/wp-content/uploads/2016/12/clin-comm-pol-16049P.pdf There are currently two licensed CFTR Fmodulators for the treatment of cystic fibrosis patients who have specific mutations mutations; Kalydeco (ivacaftor) and lumacaftor plus ivacaftor in combination (Orkambi) Whilst we acknowledge that the purpose of the guidelines is not related to commissioning; this guideline is to drive *'best practice in the diagnosis and management of cystic fibrosis*' and has an intended audience that includes '*people with cystic fibrosis, families and carers and the public'*; we contend that in its current form, these guidelines will cause considerable misunderstanding and confusion regarding the reimbursement policies currently in place and existing clinical usage of Kalydeco (ivacaftor) in England. Kalydeco (ivacaftor) is currently prescribed for over 90% of eligible patients in England, and is used by clinicians treating CF in adults and children in CF centres across England The Royal Brompton Hospital Trust (RBH)CF Service; which is the largest CF centre in England, treats over 900 non transplanted CF patients across their adult and paediatric services and has produced the following guidelines for the use of Kalydeco (ivacaftor) in their patient population RBH Paediatric Guidelines http://www.rbht.nhs.uk/healthprofessionals/clinical-departments/cystic-fibrosis/clinical-cf-guidelines-care-of-children/care-of-children-with-cystic-fibrosis-respiratory-care/ivacaftor/ RBH Adult treatment guidelines (Appendix VI) refers to the use of ivacaftor http://www.rbht.nhs.uk/healthprofessionals/clinical-departments/cystic-fibrosis/clinical-cf-guidelines-care-of-children/clinical-cf-guidelines-care-of-children-contents/ We would suggest that recommendations regarding the use of Kalydeco (ivacaftor) are published with consideration of the relevant commissioning policies and clinical use that are currently in place in England.	areas under consideration. For completeness, a recommendation referring to the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation has been added.
Vertex Pharmaceutica	Full	19	18-28	Related to comment 1; the draft guideline fails to make any mention of CFTR modulators, as a minimum, it should be explicitly stated in section 3.5 that CFTR modulators are excluded from the	Thank you for your comment. CFTR modulators were not included in the scope as current clinical practice in this area was considered to be consistent and effective, relative to the other

ls (Europe) Ltd				scope of this guidelines, and the reasons why. However, it remains preferable to follow the scope of the guidelines and in the best interests of the intended audience to include recommendations on the use of CFTR modulators in line with current clinical practise and commissioning policies.	areas under consideration. We cannot add CFTR modulators as an exclusion from the scope in section 3.5 at this stage as the scope is defined and finalised prior to guideline development. For completeness, a recommendation referring to the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation has been added.
Vertex Pharmaceutica ls (Europe) Ltd	Short	33	8-10	The current draft states '*By making robust recommendations based on the available evidence and best practise in cystic fibrosis care, this guideline will help improve care for this highly complex condition*' We would make the following comments; I. This draft does not make reference to all the available clinical evidence nor commissioning policies relating to the clinical use of Kalydeco (ivacaftor) since 2015 for the treatment of CF patients II. This draft fails to reference or include the current clinical practise where Kalydeco (ivacaftor) is routinely used for appropriate patients in CF services across England; and by failing to do so may create unnecessary confusion for clinicians and patients.	Thank you for your comment. CFTR modulators were not included in the scope as current clinical practice in this area was considered to be consistent and effective, relative to the other areas under consideration. For completeness, a recommendation referring to the NICE technology appraisal on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation has been added.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*