National Institute for Health and Care Excellence

Version 1.0 Pre-consultation

Cystic Fibrosis: diagnosis and management

Appendix N

Main appendix document

Network Metal Analysis

04 May 2017

Draft for Consultation

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologist

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Contents

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Appendix N: Network Meta-Analysis

N.1 Immunomodulatory NMA protocol

Item	Details
Review question	**What is the effectiveness of immunomodulatory agents in the management of lung disease, for example corticosteroids, azithromycin?**
Objective	• The aim of this NMA is to determine the clinical efficacy of immunomodulatory agents in reducing pulmonary inflammation in children, young people and adults with cystic fibrosis
Population	Children, young people and adults with cystic fibrosis and chronic lung disease. Patients must be clinically stable and have had no short-term (in the previous four weeks) treatment changes. Exclusion criteria: • Children <5 years of age • Confirmed allergic reaction to any of the treatments in the network • Patients receiving intermittent i.v. suppressive antimicrobial therapy • Infection with B. cepacia
Stratified analyses	• No stratifications expected
Covariates	• Covariates can be included to reduce heterogeneity where data is available. In order of importance: • Infection with P. aeruginosa • Prior exposure to study drug • Baseline values (for FEV1) • Bias (e.g. blinding)
Interventions	Any interventions considered to be immunomodulators – this may include treatments not in the review protocol as they may provide indirect evidence. Such treatments may be excluded from the rankings. **Inhaled corticosteroids**: • Beclamethosone ○ Dry powder - Low dose: <400ug/d - High dose: 400-800ug/d • Budesimide ○ Dry powder - Low dose: <800ug/d - High dose: 800-1600ug/d ○ Nebuliser suspension - Low dose: <1mg/d - High dose: 1-2mg/d • Fluticasone ○ Dry powder or aerosol inhalation - Low dose: ≤0.2mg/d - High dose: 0.21-1mg/d ○ Nebuliser suspension - dose: ≤2mg/d - High dose: 2.1-4mg/d

Item	Details

	Oral corticosteroids:
	• Prednisolone
	  ○ Oral: 1-2mg/kg
	• **Intravenuous corticosteroids**
	• Methylprednisolone
	  ○ i.v.: 10-15mg/kg for 3 days
	• **Luekatrine receptor agonists:**
	• Zafirlukast
	  ○ Oral: 40mg/d
	• Montelukast
	  ○ Oral: 5-10mg/d
	• **Dornase alfa**
	• Nebiliser suspension: 2.5-5mg/d
	• **Interferon agonists:**
	• IFN-gamma1b
	  ○ Inhaled: 500-1000ug/d
	• **Macrolide antibiotics:**
	• Azithromycin
	  ○ Low dose: ≤250mg/d on consecutive days
	  ○ High dose: 251-500mg/d on consecutive days
	NSAIDs*:*
	• Ibuprofen
	  ○ Low dose: ≤600mg/d
	  ○ High dose: 601-1600mg/d
	• Piroxicam
	  ○ Oral: 5-20mg/d
	• **Monoclonal antibodies:**
	• Omalizumab
	  ○ s.c. : max = 600mg/2wk
	Treatments will be separated into two dose categories (High and Low) either as specified by the Committee or by taking the middle value of the range given in the BNF.

Comparisons	• All interventions listed above • Combinations of those interventions • Placebo • No treatment (same class as placebo)

Outcomes	• Short-term FEV1 (change from baseline or final)
	  ○ Will include studies which report at 1-10 months
	• Long-term FEV1 (change from baseline or final)
	  ○ Will include studies which report >10 months
	• Number of exacerbations/i.v. antibiotic courses/hospital admissions for respiratory symptoms per patient within 1-10 months (preference of data used will be in the order above – N exacerbations > i.v. antibiotics > hospital admissions)
	• Number of exacerbations/i.v. antibiotic courses/hospital admissions for respiratory symptoms per patient within >10 months (preference of data used will be in the order above – N exacerbations > i.v. antibiotics > hospital admissions)

Study design	Only RCTS will be considered for inclusion. Both periods of cross over RCTs will be considered if authors have used a suitable paired analysis and if they have tested for carryover effects or have used a

Item	Details
	suitable washout period. Exclusion criteria: studies with a duration of less than 4 weeks, studies with less than two relevant treatments (non-relevant treatments include non UK licensed drugs).
Population size and directness	Studies with mixed populations (e.g. mixture of naïve and exposed patients) will be considered. Studies must have >20 participants (10 if crossover)
Search strategy	See separate document
Review strategy	• **Synthesis of data** • Network meta-analysis will be conducted using Winbugs codes (TSU Bristol Unit) • We will use mean differences (95% cr.i.) for reporting the results of continuous outcomes • We will use ORs (95% cr.i.) for reporting the results of dichotomous outcomes • We will use Rate Ratios or Mean Ratios (95% cr.i) for reporting the results of rates (depending on underlying distribution of data) • We will impute SD where it has not been reported and assess impact of this in a sensitivity analysis • We will not use MIDs as outputs will feed directly into HE model so MIDs will not be needed
Model Structure	• Class effect model o Test for similarity within classes. • We will investigate if relative treatment effects change over time. If not then we will consider pooling short and long-term outcomes. • Adjusted for covariate(s) where data allow • Use empirical priors (if available) where the ratio of studies to treatments is less than 3:1
Assumptions	• Standard NMA assumptions o Consistency o Similarity o Transitivity • Relative treatment effects do not change over time (this will be tested and model will be restructured if not valid)
Sensitivity analyses	• Long/short-term studies (if relative treatment effects do not appear to change over time) • Using studies with mixed populations • Imputed SD • Priors

N.2 Model fit characteristics

Table 1: Model fit characteristics for FEV1 % predicted after short-term treatment

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	NA	11.28	5.99	43.3
Random effects	1.26 (0.07, 4.23)[b]	9.89	8.07	44.0

(a) Compared to 10 data points
(b) Posterior for between-study standard deviation is uninformed by the data

Table 2: Model fit characteristics for FEV1 % predicted after long-term treatment

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	NA	9.85	7.99	36.0
Random effects	1.18 (0.05, 4.56)[b]	9.40	9.10	36.7

(c) Compared to 10 data points
(d) Posteroir for between-study standard deviation is uninformed by the data

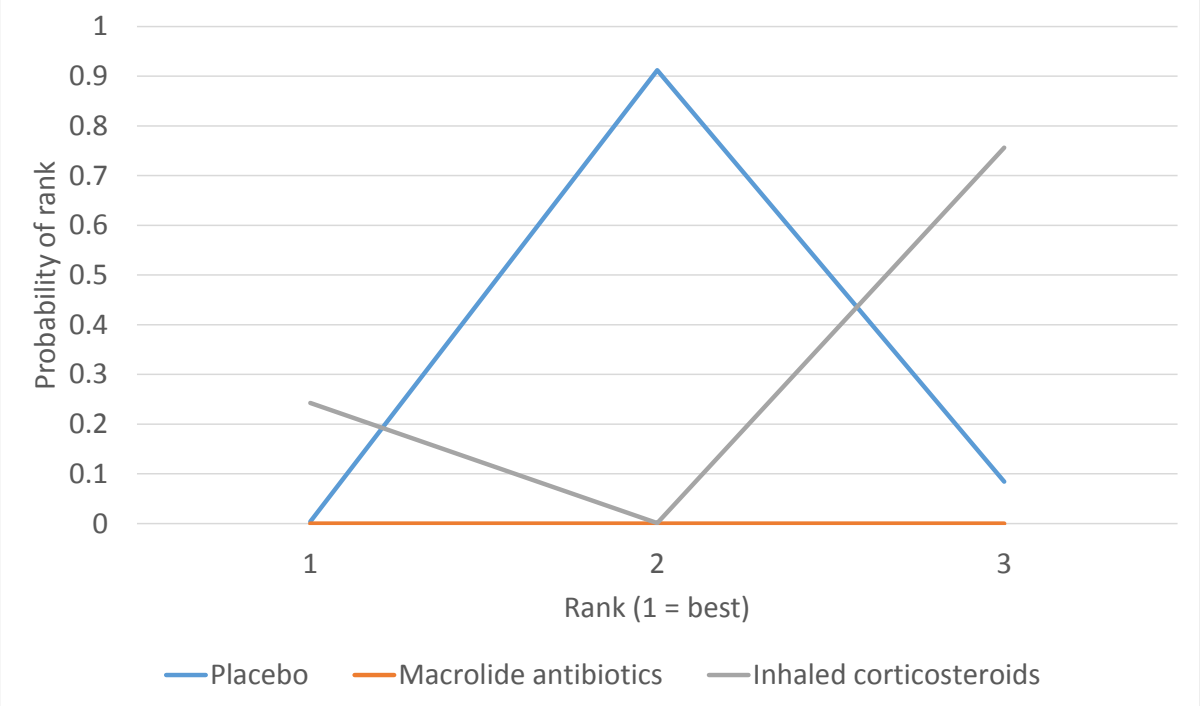
Table 3: Model fit characteristics for rate of pulmonary exacerbations after long-term treatment

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	NA	7.59	6.54	35.0

(e) Compared to 8 data points
(f) Random effects model not tested as no comparisons have multiple studies and so there is no information on between-study heterogeneity in the data

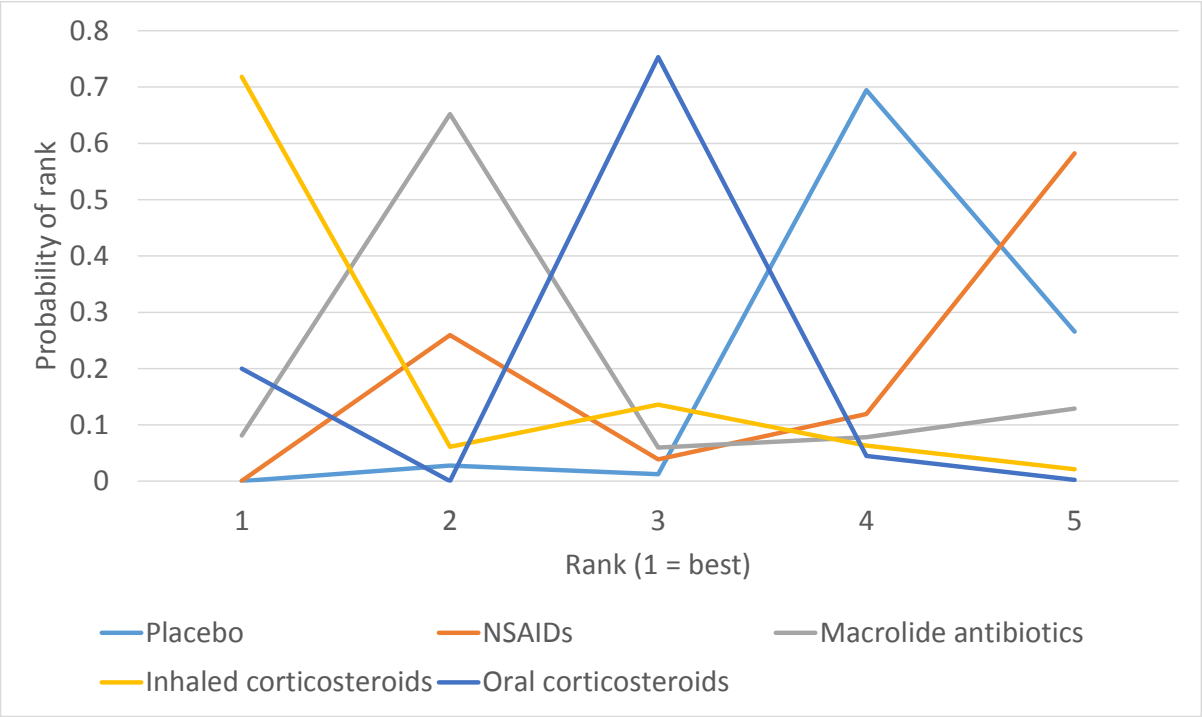
N.3 Rankograms

Figure 1: Rankogram for FEV1 % predicted after short-term treatment



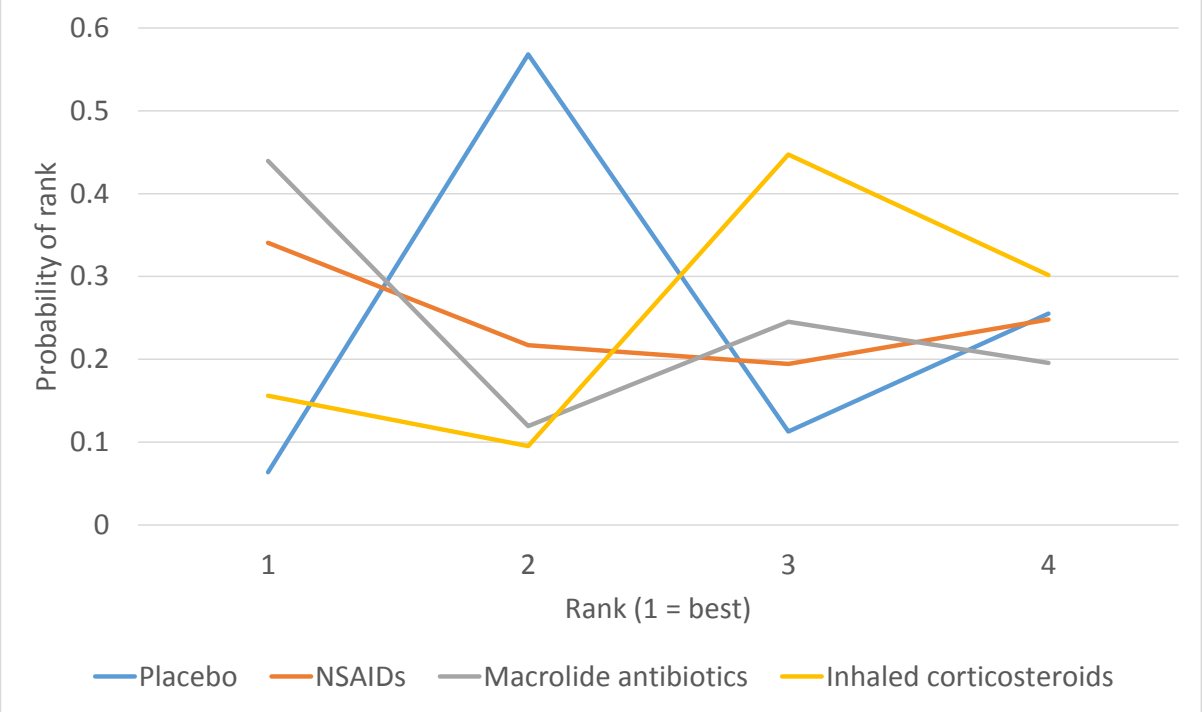
Note: Rankograms show the probability of a treatment having a particular rank. This is calculated as the proportion of iterations each treatment takes a particular rank.

Figure 2: Rankogram for FEV1 % predicted after long-term treatment



Note: Rankograms show the probability of a treatment having a particular rank. This is calculated as the proportion of iterations each treatment takes a particular rank.

Figure 3: Rankogram for rate of pulmonary exacerbations after long-term treatment



Note: Rankograms show the probability of a treatment having a particular rank. This is calculated as the proportion of iterations each treatment takes a particular rank.

N.4 Sensitivity analyses

1.1.1.1 Rate of pulmonary exacerbations - Long-term treatment

The initial NMA model for rate of pulmonary exacerbations after long-term treatment included a study of piroxicam compared with placebo (Sordelli 1994). However, the Guideline Group did not feel that this study should be included in the final analysis as it was at high risk of bias (trial was unblinded and neither randomisation nor allocation methods were sufficiently described) and was on a treatment not specified in the original review protocol. As this was the only study connecting NSAIDs to the network, the results for this class were highly sensitive to it. Removal of this study did not affect estimates for other classes in the network, but removed all estimates for NSAIDs efficacy from the final model. The results with piroxicam included are shown below:

Four studies of 354 participants were included in the network of five classes of interventions (placebo, NSAIDs, macrolide antibiotics, inhaled corticosteroids, oral corticosteroids). The inclusion of the additional study changed the quality of the evidence from low to very low. One study was at low risk of bias, one study was at high risk of bias, and for the other two the risk of bias was unclear.

Table 4 presents the results of the conventional pair-wise meta-analyses (head to head comparisons) (upper-right section of table), together with the results computed by the fixed-effects NMA for every possible treatment comparison (lower-left section of table). Both results are presented as mean differences (95% CrI).

In this analysis, long-term NSAID treatment was found to have the highest probability (66.65%) of being the best treatment to reduce the rate of exacerbations, followed by long-term macrolide antibiotic treatment (28.43%) (Table 5).

Table 4: Rate ratios (95% CrI) from conventional (white area) and network meta-analysis (grey area) for the rate of exacerbations with long-term (>10 month) treatment

	Placebo	NSAIDs	Macrolide antibiotics	Inhaled corticosteroids	Oral corticosteroids
Placebo		0.18 (<0.01, 2.13)	0.44 (0.03, 3.31)	1.34 (0.22, 9.43)	0.92 (0.08, 10.05)
NSAIDs	0.18 (<0.01, 2.13)				
Macrolide antibiotics	0.44 (0.03, 3.31)	2.52 (0.07, 269.5)			
Inhaled corticosteroids	1.34 (0.22, 9.43)	7.91 (0.34, 782.7)	3.13 (0.2, 73.28)		
Oral corticosteroids	0.92 (0.08, 10.05)	5.42 (0.15, 660)	2.13 (0.09, 65.85)	0.68 (0.03, 13.46)	

(g) Results in the top right diagonal of the table are the mean differences and 95% CrI from the conventional meta-analyses of direct evidence between the column-defined treatments compared to the row-defined treatment. Mean differences greater than 0 favour the column-defined treatment.

(h) Results in the bottom left are the mean differences and 95% CrI from the NMA model of direct and indirect evidence between the row-defined treatments compared to the column-defined treatments. Mean differences greater than 0 favour the row-defined treatment.

(i) Numbers in bold denote results for which the 95% CrI does not include the null effect of 0

Table 5: Median treatment ranking (with their 95% CrI) of all interventions in the network and the probability of being the best treatment for reducing the rate of exacerbations in the long-term (>10 months)

	Median (95% CrI) treatment rank	Probability of being the best treatment (%)
Placebo	4 (2-5)	0.62%
NSAIDs	1 (1-5)	61.15%
Macrolide antibiotics	2 (1-5)	24.72%
Inhaled corticosteroids	4 (1-5)	3.39%
Oral corticosteroids	3 (1-5)	10.12%

N.5 WinBUGS sample code

N.5.1 WinBUGS code for FEV % predicted (normal likelihood)

```
# Normal likelihood, identity link

# Fixed effects model for multi-arm trials

model{                                  # *** PROGRAM STARTS

for(i in 1:ns) {         # LOOP THROUGH THREE-ARM STUDIES

              mu[i] ~ dnorm(0,.0001)            # vague priors for all trial
baselines

    for (k in 1:na[i]) {              #  LOOP THROUGH ARMS

        var[i,k] <- pow(se[i,k],2)    # calculate variances

        prec[i,k] <- 1/var[i,k]       # set precisions

        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood

# model for linear predictor

        theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]

#Deviance contribution

        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]

      }

#  summed residual deviance contribution for this trial

    resdev[i] <- sum(dev[i,1:na[i]])

      }


totresdev <- sum(resdev[])             #Total Residual Deviance

d[1]<-0       # treatment effect is zero for reference treatment

# vague priors for treatment effects

for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }


# all pairwise mean differences

for (c in 1:(nt-1)) {

    for (k in (c+1):nt)  {
```

```
        MD[c,k]<- d[k]-d[c]
      }
  }

# all treatments to be used for ranking
for(k in 1:nt){ dR[k] <- d[k] }
# ranking on relative scale
for (k in 1:ntR) {
    rk[k]<- (ntR+1)-rank(dR[],k)     # events are "good"
#    rk[k]<- rank(dR[],k)             # events are "bad"
    best[k] <- equals(rk[k],3)       # rank=4 is best
#calculate probability that treat k is h-th best
    for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
  }
}                                    # *** PROGRAM ENDS
```

N.5.2 WinBUGS code for rate of exacerbations (Poisson likelihood)

```
# Poisson likelihood, identity link
# Fixed effects model for multi-arm trials at the class level
model{                               # *** PROGRAM STARTS
for(i in 1:ns){                      #   LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.001)           # vague priors for all trial baselines
    for (k in 1:na[i]) {             #  LOOP THROUGH ARMS
                           y[i,k] ~ dpois(theta[i,k])
# Model the linear predictor ON THE LOG SCALE
        log(theta[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Poisson Deviance contribution
        dev[i,k] <- 2*((theta[i,k]-y[i,k])+(y[i,k]*(log(y[i,k] / theta[i,k]))))
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] <- md[i,k]
# mean of LMR distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
```

```
# adjustment, multi-arm RCTs

        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])

# cumulative adjustment for multi-arm trials

        sw[i,k] <- sum(w[i,1:k-1])/(k-1)

      }

  }

totresdev <- sum(resdev[])            #Total Residual Deviance

d[1]<-0       # treatment effect is zero for control arm

# vague priors for treatment effects

for (k in 2:nt){  d[k] ~ dnorm(0,.001) }

# all pairwise mean differences

for (c in 1:(nt-1)) {

    for (k in (c+1):nt)  {

        RR[c,k]<- exp(d[k]-d[c])

      }

  }

# all treatments to be used for ranking

for(k in 1:nt){ dR[k] <- d[k] }

# ranking on relative scale

for (k in 1:ntR) {

#    rk[k]<- (ntR+1)-rank(dR[],k)     # events are "good"

    rk[k]<- rank(dR[],k)             # events are "bad"

    best[k] <- equals(rk[k],1)       # rank=1 is best

#calculate probability that treat k is h-th best

    for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }

  }

}                                    # *** PROGRAM ENDS
```

N.6 Antimicrobials Chronic NMA methods

For number of patients with ≥1 exacerbation, empirical priors for heterogeneity were used for RE models (Turner 2012). Exacerbations were considered to be semi-subjective due to the heterogeneity of our definition of exacerbation as a strictly defined exacerbation, hospital admission for respiratory symptoms or course of i.v. antimicrobial therapy. The prior distribution used for between-study variance was a log-normal distribution with mean -3.02 and variance 3.423.

N.7 Imputation of missing standard errors for FEV^1 % predicted

Standard errors (SE) for the change from baseline were imputed for studies which did not report a measure of uncertainty/variance, or for those where this could not be calculated from the information reported in the study. Estimating SE by assuming a common standard

deviation (SD) across the studies, informed by studies for which SE can be calculated (Stevens 2011).

- Population SD was estimated to be 17.73 (95% CrI: 13.38, 21.58) for short-term FEV and 10.87 (95% CrI: 3.43, 12.94). Missing study values were imputed using WinBUGS.

N.8 Antimicrobials Chronic NMA protocol

Item	Details
Review question	**What is the effectiveness of antimicrobial treatment to treat chronic pulmonary infection with P. aeruginosa?**
Objective	• The aim of this NMA is to determine the clinical efficacy of different antimicrobial agents for the treatment of chronic pulmonary infection with P. aeruginosa in children and young people with cystic fibrosis
Population	• Children, young people and adults with cystic fibrosis and chronic pulmonary infection by Pseudomonas aeruginosa. Patients must be clinically stable and have had no short-term (in the previous four weeks) treatment changes. • Chronic pulmonary infection defined either by: ○ Copenhagen definition (Hoiby et al. 1977) – persistent presence of P. aeruginosa for at least 6 consecutive months, or less when combined with the presence of >=2 P. aeruginosa precipitating antibodies ○ Leeds criteria (Lee et al. 2003) – when >50% of months where samples have been taken have a positive P. aeruginosa culture. • Exclusion criterion: unidentified infection, infection with B. cepacia complex, children <5 years of age, patients receiving intermittent i.v. suppressive antimicrobial therapy, confirmed allergic reaction to any of the treatments in the network
Stratified analyses	• No stratifications expected
Subgroup Analyses	• If there is a lot of heterogeneity in the data then we will examine subgroup analyses by the following variables: • Route of administration
Covariates	• Covariates can be included to reduce heterogeneity where data is available. In order of importance: • Prior exposure to study drug • Baseline values (for FEV1) • Bias (e.g. blinding)
Interventions	• Treatments may differ in route of administration (code as separate treatments if so) • Aminoglycoside ○ Amikacin ○ Tobramycin • Beta-lactam ○ Aztreonam lysine (class) ○ Carbenicillin • Broad Spectrum ○ Fosfomycin • Colamycin ○ Colamycin • Macrolide Antibiotics ○ Azithromycin (high dose): >500mg/d • Polymyxin ○ Colistimethate sodium • Quinilones

Item	Details
	○ Ciprofloxacin Minimum/maximum dose range should be specified in detail for included treatments, as well as what would be considered high/low dose. Low/high dose will need to be specified by the Committee for each antimicrobial.
Comparisons	• All interventions listed above • Combinations of those interventions • Placebo • No treatment (same class as placebo)
Outcomes	• Primary: • Short-term FEV1(change from baseline or final) ○ Will include studies which report at 4-10 weeks • Long-term FEV1 (change from baseline or final) ○ Will include studies which report at 10-52 weeks • Number of patients with >1 exacerbation/hospital admission for respiratory symptoms) within 4-10 weeks • Number of patients with >1 exacerbation/hospital admission for respiratory symptoms within 10-52 weeks • Suppression of P. aeruginosa
Study design	• Only RCTS will be considered for inclusion. Both periods of cross over RCTs will be considered if authors have used a suitable paired analysis and if they have tested for carryover effects or have used a suitable washout period. • Exclusion criteria: studies with a duration of less than 4 weeks, studies with less than two relevant treatments (non-relevant treatments may include non UK licensed drugs).
Population size and directness	Studies with mixed populations (e.g. mixture of naïve and exposed patients) will be considered under the following assumptions: • We will only include mixed population studies if more than 2/3 of the sample falls within the pre specified strata. • If a study reports an unconfirmed organism in more than 80% of participants then we will exclude. • Studies must have >20 participants (10 if crossover)
Search strategy	See separate document
Review strategy	• Synthesis of data: • Network meta-analysis will be conducted using Winbugs codes (TSU Bristol Unit) • We will use mean differences (95% CrI) for reporting the results of continuous outcomes • We will use ORs (95% CrI) for reporting the results of dichotomous outcomes • We will use rate ratios or mean ratios (95% CrI) for reporting the results of rates (depending on underlying distribution of data) • We will impute SD where it has not been reported and assess impact of this in a sensitivity analysis • We will not use MIDs as outputs will feed directly into HE model so MIDs will not be needed
Model Structure	• Class effect model: ○ We will test for within-class variability to assess if a class model is appropriate ○ Assume similarity within classes but do not assume same efficacy – we are still interested in treatment effects. Therefore model cannot have fixed class effects • We will investigate if relative treatment effects change over time. If not then we will consider pooling short and long-term outcomes.

Item	Details
	• Adjusted for covariate(s) where data allow • Use empirical priors (if available) where the ratio of studies to treatments is less than 3:1
Assumptions	• Classic NMA assumptions ○ Consistency ○ Similarity ○ Transitivity • If mucolytics and immunomodulatory agents are included as covariates we assume that there is no multiplicative effect of them with the different antibiotics (i.e. that they have the same effect themselves regardless of which antibiotic is used in addition)
Sensitivity Analyses	• Treatment characteristics that have not been stratified/subgrouped (e.g. dose – high/low, route of administration if there is not enough data for subgroup analysis) • Long/short-term studies (if relative treatment effects do not appear to change over time) • Imputed SDs

N.9 Model fit characteristics

Table 6: Model fit characteristics for pulmonary exacerbations after short-term treatment

Model	Between-study standard deviation, median (95% CrI)	Residual deviance, mean (95% CrI) [a]	pD	DIC
Fixed effects	NA	6.48 (1.54, 15.25)	5.936	34.930
Random effects	1.40 (0.05, 4.71)	6.28 (1.65, 16.08)	6.583	36.050

(j) Compared to 6 data points

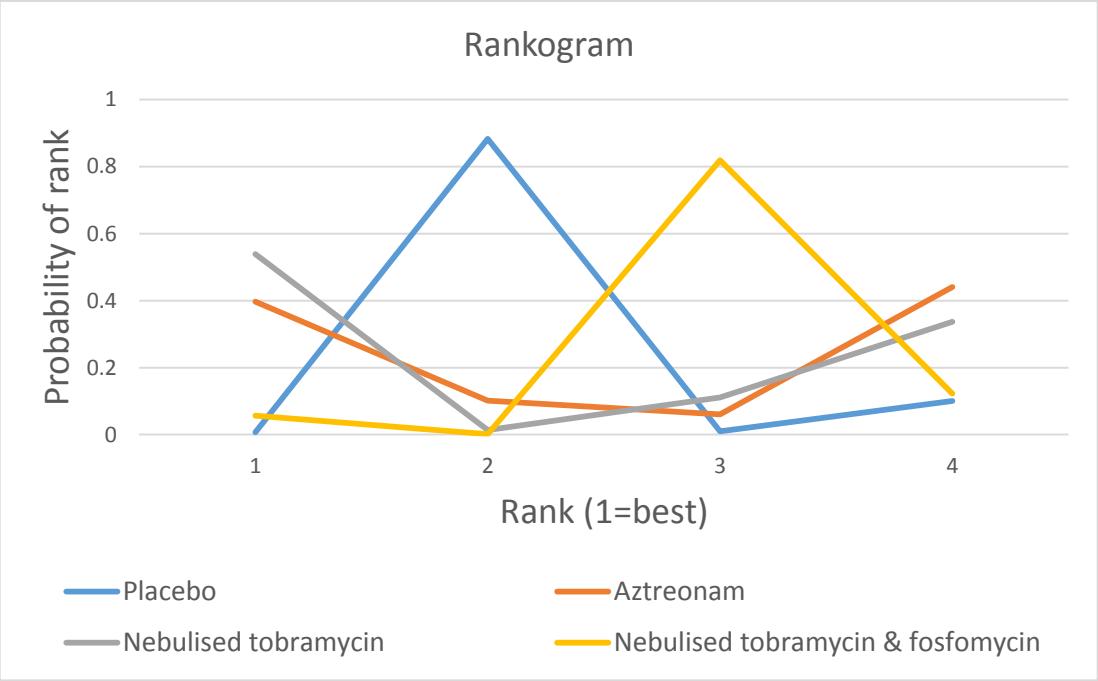
Table 7: Model fit characteristics for pulmonary exacerbations after long-term treatment

Model	Between-study standard deviation, median (95% CrI)	Residual deviance, mean (95% CrI) [a]	pD	DIC
Fixed effects	NA	17.26 (10.04, 28.2)	11.042	89.459
Random effects	1.69 (0.21, 5.64)	12.18 (4.47, 23.61)	12.117	85.447

(k) Compared to 12 data points

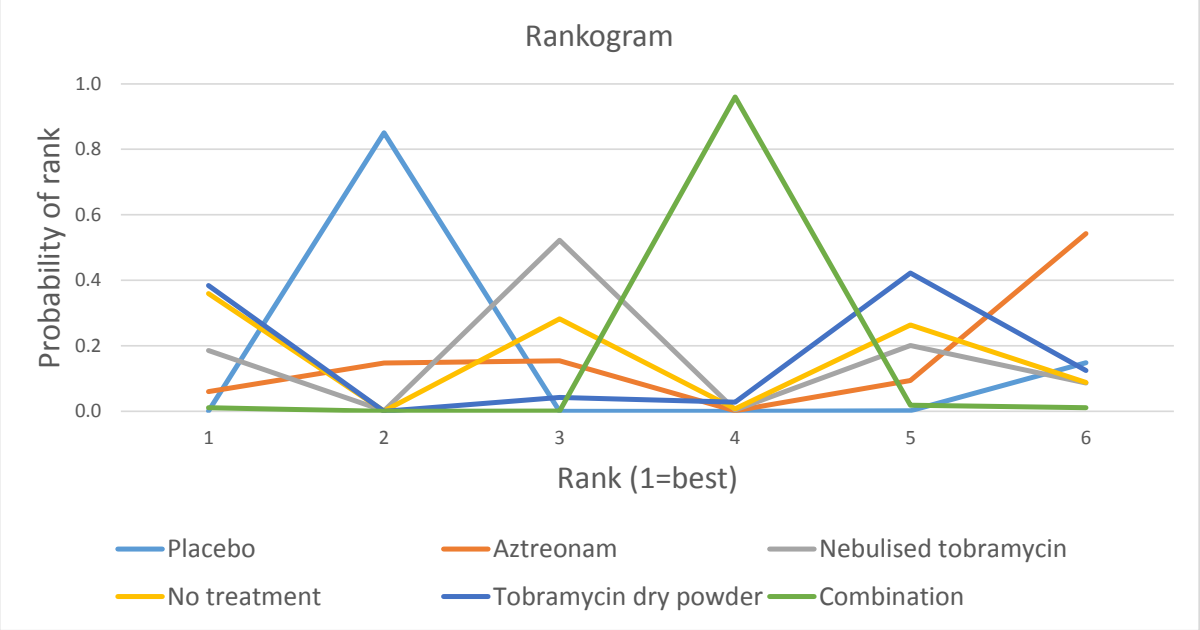
N.10 Rankograms

Figure 4: Rankogram for pulmonary exacerbations after short-term treatment



Note: Rankograms show the probability of a treatment having a particular rank. This is calculated as the proportion of iterations each treatment takes a particular rank.

Figure 5: Rankogram for pulmonary exacerbations after long-term treatment



Note: Rankograms show the probability of a treatment having a particular rank. This is calculated as the proportion of iterations each treatment takes a particular rank. Combination: 28 days aztreonam lysine (nebulised) alternating with 28 days tobramycin (nebulised)

N.11 WinBUGS sample code

N.11.1 Pulmonary exacerbations after long-term treatment

```
# Binomial likelihood, logit link
# Trial-level data given as single arms AND treatment differences
# Fixed effects (treatment-level) model for multi-arm trials
# Treatment level only (no class-level)
model{                                  # *** PROGRAM STARTS
for(i in 1:ns) {        # LOOP THROUGH THREE-ARM STUDIES
             mu[i] ~ dnorm(0,.0001)           # vague priors for all trial
baselines
    for (k in 1:na[i]) {             #  LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
            +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])

      }

totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
# all pairwise mean differences
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        OR[c,k]<- exp(d[k]-d[c])
      }
  }
# all treatments to be used for ranking
for(k in 1:nt){ dR[k] <- d[k] }
# ranking on relative scale
```

```
for (k in 1:ntR) {
#    rk[k]<- (ntR+1)-rank(dR[],k)      # events are "good"
    rk[k]<- rank(dR[],k)              # events are "bad"
    best[k] <- equals(rk[k],1)        # rank=1 is best
#calculate probability that treat k is h-th best
    for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
  }
}                                      # *** PROGRAM ENDS
```