

Appendix 3: SUMMARY OF RESEARCH RECOMMENDATIONS

<b>Research Recommendation in Guideline</b>	<b>Suggested Research Title:</b> (e.g. What is the clinical and cost effectiveness of...)	<b>Patient Group</b>	<b>Intervention</b>	<b>Comparator</b>	<b>Outcomes</b>	<b>Why would this research be important?</b> (for the public, patients or the NHS)
Further research, over a longer period, is needed to further investigate the role of long-term macrolide therapy in reducing exacerbations of asthma.	Are there continuing benefits from long term low dose macrolides in asthma?	Patients with asthma	Long term low dose macrolide therapy over an extended period of greater than 1 year	Standard asthma therapy	Exacerbation rate, symptoms, quality of life, effects on microbiome	Although macrolide therapy appears to be helpful over up to 12 months the effects beyond this point are unknown
Use of validated scoring systems and consideration of creation of a core outcome set should be considered in future trials of macrolide therapy in asthma to allow more accurate delineation of clinical response and comparison between studies.	Consensus criteria for a core outcome dataset and measurement methodology in future trials of macrolides in asthma					
Head to head comparisons of	Comparison of dosing regimens for long term	Patients with	Various dosing regimens of	Alternate dosing	Exacerbation rate, symptoms,	To inform the best dosing regimen to

different macrolide therapy and of differing dose regimes for the same macrolide are required to optimise the use of macrolide therapy in asthma	low dose macrolides in asthma	asthma	different macrolides e.g azithromycin 500mg thrice weekly vs 250mg daily	regime	quality of life, effects on microbiome, side effects	optimise benefits vs side effects
Research into the discrepancy between significant reductions in inflammation but minimal improvements in clinical parameters is required.	Relationship between inflammation and symptoms in asthma	Patients with asthma	Observational study. Measurement of inflammatory markers and symptoms	None	Correlation between markers of inflammation and symptoms in asthma	To better understand pathophysiological mechanisms of asthma and patient symptoms
Research into the impact of macrolide therapy in different clinical phenotypes of asthma should be performed in order to assess whether greater benefit is seen in one phenotype over another.	Response to long term low dose macrolide therapy in different asthma phenotypes	Patients with asthma separated into different phenotypes e.g eosinophilic vs non-eosinophilic	Long term low dose macrolide therapy	Different asthma phenotypes	Exacerbation rate, symptoms, quality of life, effects on microbiome	To enable better targeting of therapy at those most likely to benefit and to avoid giving therapy to those unlikely to benefit
Research into the overlap between asthma and bronchiectasis and the	Suggest removing this as covered by recommendation above – will also need					

<p>impact of this on response to macrolides may assist in identifying asthma phenotypes which may respond differently to macrolide therapy</p>	<p>to remove from body of document</p>					
<p>Long-term studies of microbiological impact of prolonged macrolide therapy in bronchiectasis</p>	<p>Impact of long term low dose macrolide therapy on sputum microbiology in bronchiectasis</p>	<p>Patients with bronchiectasis</p>	<p>Long term low dose macrolide therapy with microbiological surveillance of sputum before, during and after therapy</p>	<p>Microbiological surveillance in patients not having long term low dose macrolide therapy</p>	<p>Changes in sputum microbiology</p>	<p>Will help to discover any potential adverse consequences of long term low dose macrolides</p>
<p>Head-to-head comparison of different dose regimens for the same macrolide in bronchiectasis</p>	<p>Comparison of dosing regimens for long term low dose macrolides in bronchiectasis</p>	<p>Patients with bronchiectasis</p>	<p>Various dosing regimens of different macrolides e.g azithromycin 500mg thrice weekly vs 250mg thrice weekly</p>	<p>Alternate dosing regimen</p>	<p>Exacerbation rate, symptoms, quality of life, effects on microbiome</p>	<p>To inform the best dosing regimen to optimise benefits vs side effects</p>
<p>Head-to-head comparisons of different macrolides (e.g. azithromycin vs erythromycin).</p>	<p>Comparison of long term low dose azithromycin or erythromycin in bronchiectasis</p>	<p>Patients with bronchiectasis</p>	<p>Long term low dose treatment with different macrolides</p>	<p>Alternative macrolide</p>	<p>Exacerbation rate, symptoms, quality of life, effects on microbiome</p>	<p>To determine the most effective macrolide for long term low dose treatment of bronchiectasis</p>

Prolonged studies of benefit and risk beyond 12 months of use.	Are there continuing benefits from long term low dose macrolide therapy in bronchiectasis?	Patients with bronchiectasis	Treatment with long term low dose macrolides beyond 12 months	Standard therapy	Exacerbation rate, symptoms, quality of life, effects on microbiome	Although macrolide therapy appears to be helpful over up to 12 months the effects beyond this point are unknown
Studies assessing the effect of macrolides following re-introduction of therapy following a break.	Does a break in long term low dose macrolide therapy reduce efficacy of treatment in bronchiectasis?	Patients with bronchiectasis on long term low dose macrolide therapy	Patients given a break from macrolide therapy of 3 months in every 12 months of treatment	Patients on continuous therapy	Exacerbation rate, symptoms, quality of life, effects on microbiome	To determine if breaks in therapy are helpful or harmful
Use of bronchiectasis specific quality of life measures in macrolide trials.	Consensus criteria for disease specific QoL measures in b'ectasis research					
Comparison of outcomes in patients with different baseline exacerbation rates when treated with macrolides.	How bad do you need to be to benefit from macrolides in bronchiectasis?	Patients with bronchiectasis divided into groups with different exacerbation rates	Long term low dose macrolide therapy	Various cohorts by exacerbation frequency (eg up to one exacerbation a year, 2-3 a year, more than 3 a year)	Exacerbation rate, symptoms, quality of life, effects on microbiome	To determine patients who will get most benefit from macrolides
Comparison of outcomes in patients with different baseline	Response to long term low dose macrolides in bronchiectasis with	Patients with bronchiectasis grouped according	Long term low dose macrolide	Various groups defined by entry microbiology	Exacerbation rate, symptoms, quality of life,	To determine effect of baseline microbiology on

microbiological culture/microbiome profiles when treated with macrolides.	different colonising organisms	to baseline microbiology	therapy	(e.g. pseudomonas vs others)	effects on microbiome	response to long term low dose macrolides
Comparison of outcomes in patients with different baseline quality of life scores when treated with macrolides.	Response to long term low dose macrolides in bronchiectasis patients with different baseline quality of life measures	Patients with bronchiectasis grouped according to baseline quality of life measures	Long term low dose macrolide therapy	Various groups defined by baseline quality of life scores	Exacerbation rate, symptoms, quality of life, effects on microbiome	To determine effect of baseline quality of life on response to long term low dose macrolides
Comparison studies of long-term macrolides to other oral or inhaled prophylactic regimens.	What is the best prophylactic strategy in bronchiectasis/	Patients with bronchiectasis	Long term low dose macrolide therapy	Other oral or inhaled antibiotic prophylactic therapy	Exacerbation rate, symptoms, quality of life, effects on microbiome, side effects	To determine best therapeutic strategy for prophylactic antibiotics in bronchiectasis
Studies looking into the benefits of combined macrolide and inhaled antibiotic regimens.	Mono or dual antibiotic prophylaxis in bronchiectasis – which is best?	Patients with bronchiectasis	Long term low dose macrolide therapy	Long term low dose macrolide therapy in combination with an inhaled antibiotic	Exacerbation rate, symptoms, quality of life, effects on microbiome, side effects	To determine best therapeutic strategy for prophylactic antibiotics in bronchiectasis
Long term (>12 months) follow up trials to evaluate impact of long-term macrolide therapy on mortality, antimicrobial	Are there continuing benefits from long term low dose macrolide therapy in bronchiectasis?	Patients with bronchiectasis	Long term low dose macrolide therapy for > 12 months	Standard treatment	Exacerbation rate, symptoms, quality of life, effects on microbiome, side effects	Although macrolide therapy appears to be helpful over up to 12 months the effects beyond this point are

resistance, long term potential cardiac toxicity and disease progression.						unknown
Studies to evaluate the impact of short-term breaks in chronic therapy with long term macrolide antibiotics are needed.	Long term low dose macrolide therapy in bronchiectasis, time for a break?	Patients with bronchiectasis	Long term low dose macrolide therapy with breaks of 3 months in every 12	Continuous long term low dose macrolide therapy	Exacerbation rate, symptoms, quality of life, effects on microbiome, side effects	To determine if breaks in therapy are helpful or harmful
Studies phenotyping COPD in large trials where subgroup analysis can potentially identify groups of patients with COPD who will benefit most from long term macrolide therapy.	Long term low dose macrolides in COPD, who benefits most	Patients with COPD divided into different phenotypes (e.g. by exacerbation rate, microbiology, etc)	Long term low dose macrolide therapy	Various groups defined by baseline phenotype	Exacerbation rates, hospitalisation, quality of life, effects on microbiome	To determine patients who will get most benefit from macrolides
Trials investigating head to head the benefits and adverse effects of oral agents that reduce acute exacerbations in patients with COPD (long term low dose macrolides, carbocysteine, roflumilast)	Exacerbation reduction in COPD, which drug is best?	Patients with COPD	Long term low dose macrolide therapy	Alternatives such as roflumilast, carbocysteine	Exacerbation rates, hospitalisation, quality of life	To determine the best exacerbation reduction strategy for patients with COPD
High quality, adequately	Effect of long term low	Patients with	Long term low	Standard	Cough	To determine if

powered randomised trials are needed to assess the effect of macrolides on outcomes of importance in chronic cough.	dose macrolides in patients with chronic cough	chronic cough	dose macrolides	therapy	frequency, quality of life	long term low dose macrolides are helpful in treating chronic cough