OSAC TRIAL:
FREQUENTLY ASKED CLINICAL QUESTIONS

Q.	**Why consider oral steroids for coughs for which antibiotics would not typically be prescribed, i.e. self-limiting viral infections?**
A.	We want to know if corticosteroids could help to dampen unwanted effects of respiratory tract inflammation associated with acute bronchitis - which shares some clinical / pathological characteristics with asthma. If we find 40mg prednisolone daily is effective, we will not be concluding that this should be the new treatment of choice, but recommending that further trials of lower dose oral, or high (or medium) dose inhaled steroids should be conducted. The rationale of the OSAC trial is therefore **proof of concept**.
Q.	**40mg prednisolone for 5 days is a high dose regimen. How safe is this intervention?**
A.	This dose has been selected to ensure that we detect a response if there is one. Similar doses of corticosteroids are already in routine clinical use for treatment of acute croup (no concurrent antibiotics) and have been shown effective for acute pharyngitis (with concurrent antibiotics). We believe that this intervention is as safe as it is for acute asthma. Side effects are uncommon – see the protocol and patient information booklet for a list of potential side effects and their incidences compared to placebo in a recent study of the use of prednisolone for Bells palsy.
Q.	**The list of exclusion criteria underline that this intervention affects most body systems!**
A.	True. These meds have systemic effects if taken long term (> 2 weeks). But short term (< 1 week), high dose prednisolone is relatively safe. The eligibility criteria have been designed to select a group of patients who are relatively well, in whom we anticipate the least risk to health.
Q.	**I am concerned that patients may be harmed by the trial medicine. Steroid psychosis is rare but it does happen, and it would be disastrous if this happened to a patient who had taken medicine for a trial. How can we ensure this does not happen?**
A.	We know that steroid psychosis is rare but unfortunately there is very little evidence about its incidence. We are aware of two studies which conclude that mild and reversible mood and cognitive changes appear common during steroid treatment, but that more studies are needed to determine the incidence of steroid-induced psychosis. Patients who have a current or previous history of severe affective disorders, e.g. manic depression, or previous steroid psychosis, are excluded from taking part in OSAC.
Q.	**I am concerned that the trial medicine may induce diabetic ketoacidosis.**
A.	Diabetic ketoacidosis is a rare but very serious potential side affect of steroids. We found one Danish study estimating the annual incidence of diabetic ketoacidosis at 12.9 per 100,000 people, but this did not include any data for diabetic ketoacidosis episodes precipitated by steroids. As a routine part of the trial, patients will be monitored closely and advised to report any health concerns to their GP.
Q.	**Steroids are harmful in pregnancy…**
A.	We did not find any evidence of harm to the unborn child from steroids. Where there is a medical indication for their use, the BNF states that “the benefits of treatment with corticosteroids during

	pregnancy and breastfeeding outweighs the risk" and that "88% of prednisolone is inactivated as it crosses the placenta. However, despite this women who are currently breastfeeding, known to be pregnant, trying to conceive or at risk of pregnancy (e.g. unwilling to take a reliable form of contraception) in the next month are excluded from taking part in OSAC.
Q.	**Is it not counter-inuitive to give steroids, which can weaken the immune system, to a patient with a chest infection?**
A.	We expect that a short course of oral steroids at the OSAC trial dose (40mg per day for 5 days) will not have compromise the immune system of an eligible patient. Patients with known immune-deficiency of any kind are not eligible to take part in the OSAC trial.
Q.	**Why is the list of exclusion criteria so extensive? Why exclude people on the basis of osteoporosis, or recent exposure to herpes zoster if they have not previously had chickenpox?**
A.	Many of the exclusion criteria, especially the list A-P on p2 of CRF1 (face-to-face eligibility assessment) refer to conditions which are made worse by exposure to steroids, e.g. osteoporosis, epilepsy, ocular herpes simplex, and chickenpox. Because we are testing a relatively high dose in OSAC, it is necessary to exclude all patients with such conditions, to ensure patient safety. (Don't forget that, even if the results of the OSAC trial turn out to be positive, we will NOT be advocating 40mg prednisolone for 5 days as an appropriate treatment option.)
Q.	**What if one of my patients has one of these problems but as yet <u>undiagnosed</u>, e.g. DM or peptic ulcer?**
A.	As in any trial, all patients will be asked to see their GP if they have any health concerns. They will be closely monitored throughout via the symptom diary and weekly contact by the OSAC Research Nurse.
Q.	**What about undiagnosed COPD? Some asthma studies exclude patients with a 10 year pack history as they possibly have a degree of COPD. Why not exclude them from OSAC?**
A.	If you *strongly* suspect COPD clinically, then we suggest excluding such patients, but a 10 year pack history on its own is not sufficiently sensitive and specific to diagnose COPD. We will be reviewing patients' medical records 3 months after trial participation so we can ascertain any in whom you subsequently diagnose COPD (and asthma) to see if excluding them from the analyses makes an difference to our estimates of the treatment effects.
Q.	**Should I recruit the 60 year old smoker who presents with an acute cough of three weeks duration in whom I suspect lung cancer?**
A.	Yes. We definitely want to include these patients. GPs should continue to investigate for lung cancer as per usual practice / DoH guidelines. If the patient receives a diagnosis of lung cancer within the trial period (3 months from recruitment), this may need to be reported to the trial team as a <u>Serious Adverse Event</u> (SAE), depending on the specific details of the diagnosis (i.e. if it meets the criteria defining a SAE), and patients should not be routinely withdrawn.
Q.	**Could this research lead to increasing rather than decreasing medicalisation of viral infections?**

A.	We do not wish to medicalise acute bronchitis with oral steroids! However, current antibiotic treatment options are (i) ineffective, and (ii) medicalising. This trial is one attempt to find a 'least worst' option for chest infections, both for patients and for the NHS. If the OSAC trial shows prednisolone to be effective for acute cough, further research into lower dose oral steroids, or inhaled steroids, will be recommended. Trial patients will be given to understand that, even if the trial works well for them, they should not routinely expect GPs to subsequently use oral steroids for similar future infections.
Q.	**If this research detects a positive effect of steroids on cough symptom severity and/or duration, more and more patients in the future will expect to consult and to be prescribed steroids for acute cough. What impact will that have on my workload as a GP?**
A.	Firstly, the OSAC trial does not seek to encourage patients to consult or to expect medicines. It aims to find out whether steroids could be one strategy in the greater endeavour to reduce the real future danger of unmanageable multi-antimicrobial resistance in the community. If a positive effect is seen for oral steroids, then further research will be needed to demonstrate the effectiveness of inhaled steroids. At a societal level and in the long term, the economy may benefit if people are able to treat their cough with an over-the-counter inhaled steroid which means they feel better sooner and have to take fewer days off work.
Q.	**Would you or I be willing to take 40mg prednisolone for 5 days?**
A.	Antibiotic resistance is a serious threat to future health [see BBC news article "Antibiotics resistance 'as big a risk as terrorism' - medical chief"http://www.bbc.co.uk/news/health-21737844]. We badly need alternatives to help patients with an illness that typically lasts 3 weeks and leaves many struggling to cope with daily living. Steroids ***may*** be one part of the answer...
Q.	**Why are you excluding patients who have taken any asthma medication within the last five years? This means excluding patients who (for example) receive a short course of inhaled steroids four years ago for a wheezy cough.**
A.	The purpose of this 5 year exclusion criterion for any asthma medication is so that we do not inadvertently include patients with asthma, in whom we would expect steroids to be effective. We will therefore stick with this criterion as currently stated, but monitor the screening logs and review if this is a common reason to exclude patients.
Q.	**Wheeze is one of the four presenting symptoms indicating potential eligibility. Is wheeze not primarily an indication of asthma?**
A.	Wheeze, cough and shortness of breath are hallmark symptoms of asthma, but also frequently occur in patients with acute chest infections, especially during outbreaks of so-called 'atypical' infections such as those due to *Mycoplasma pneumonia* and *Chlamydia pneumonia*. We therefore wish to include patients with these symptoms in the OSAC trial, but we will review patients' medical records 3 months after trial participation so we can ascertain any in whom you subsequently diagnose asthma (and COPD) to see if excluding them from the analyses makes any difference to our estimates of the treatment effects.

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Q.	**Will the investigators be assessing reversibility based on wheeze?**
A.	Yes, among others, we are asking patients to record the following symptoms in their symptom diaries: cough, shortness of breath, wheeze and peak flow. This will give us the opportunity to evaluate the effects of steroids on these as well as other systemic symptoms.
Q.	**If I'm unsure whether a patient will need antibiotics within the next day or two, should I recruit them?**
A.	Patients who need, in the view of the Responsible Clinician, an immediate antibiotic script are not eligible to take part in the trial. However, if the clinician is clinically comfortable in giving the patient a prescription delayed until at least the day following recruitment, this does not preclude the patient from taking part. The key points are that the patient should be managed in line with your normal practice, and that patients with delayed prescriptions should initiate their trial treatment before cashing in their antibiotic prescription.
Q.	**As patients with a "current or previous history" of "peptic ulcer disease" are excluded (point 15, Exclusion Criteria, CRF Section 1), should patients on ACE (angiotensin-converting-enzyme) inhibitors also be excluded?**
A.	Patients on ACE do not need to be excluded. However, as ACE inhibitors can cause cough, patients must have evidence of lower respiratory tract infection (sputum, wheeze, chest pain etc) - as per point 3, Inclusion Criteria, CRF Section 1.