



Protocol Version 8 26 09 07

1. Title: DEcision rule for severe Symptoms and Complications of Acute Red Throat in Everyday practice (DESCARTE)

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2. Importance:

2.1 The burden of sore throat and the use of antibiotics. Respiratory Tract Infections (RTIs) still exceed back pain as a the major cause of work days lost to illness¹. Upper respiratory tract illness (URTI) is also the commonest respiratory illness experienced by the general population in developed countries: in addition to the millions of NHS Direct contacts, at least 6 million people see their GP every year with sore throat^{2 4 5} – costing the NHS an estimated £25 million annually in consultation costs alone, an additional £6-12 million in prescribing costs^{4 5}, and the costs and morbidity associated with quinsy and other complications⁶. Antibiotic use in England has decreased from approximately 44 million items to 33 million items (i.e. a 25% reduction) since 1996, but the reduction has stalled (www.ppa.org), and prescribing is still double the rate of other northern European countries. Antibiotic resistance is still a major potential threat to public health, and community prescribing of antibiotics fuels the development and spread of resistant organisms – which will lead to many serious infections becoming untreatable^{7;8}. The key to maintaining the precious resource of our limited pool of antibiotics is to reduce antibiotic use further for those not needing antibiotics, whilst not denying those patients at risk of severe illness or complications the benefit from antibiotics. A further reduction in antibiotic use is also only likely to happen if both patients' and GPs' concerns about the danger of complications and severe illness can be addressed⁹. To meet these concerns, we need better knowledge about those who are likely to benefit significantly from antibiotics and those who are not. The most robust method to address this issue is a large prospective cohort – to provide unbiased prospective clinical assessment and to avoid the potential recall bias in case control designs. High volume data collection becomes feasible if the recruitment of GPs, recruitment of patients, and data collection are all very simple - which is what is proposed in the current study.

This study will thus provide key clinical information to improve patient care for one of the commonest conditions managed in the NHS. It will also develop methodology in primary care – methodology for most efficiently recruiting and coordinating a large cohort of GPs using existing Research Network infrastructure, and for developing and assessing clinical prediction rules in large cohorts.

2.2 Issues surrounding antibiotic prescribing for sore throat: GP beliefs. Our group has recently completed two pieces of work to identify the current issues for GPs.

a) **Quantitative evidence.** A quantitative cross sectional survey of 500 GPs which shows beliefs about the effectiveness of antibiotics for symptoms and complications are closely related, and beliefs are still the major predictors of prescribing. To explore in detail some of the issues underlying attitudes to prescribing antibiotics further qualitative work was needed:

b) **Qualitative evidence.** A grounded theory study of GPs assessed in detail the current context, issues, and concerns of GPs about antibiotic use for sore throat⁹. The qualitative data supported the survey evidence, and showed that

- 1) All GPs believe antibiotics are useful for some people, but are uncertain about who benefits
- 2) GPs manage this uncertainty by rationalising their targeting of antibiotics for those who they believe have 'bacterial' infections, or who they believe are at increased risk of severe illness or complications, but few were aware of the Centor criteria (fever, pus, the absence of cough, lymph nodes) which predict the presence of *Streptococci*¹⁰. Each GP uses different clinical features to target antibiotic prescribing (e.g. worsening illness, fever, myalgia, looking unwell, headache, appearance of the pharynx, cervical lymph nodes, social context).

Thus before antibiotic use can be improved, research is needed to clarify key pieces of evidence i.e. to assess a) which subgroups of patients are at risk of adverse outcome (prolonged or severe illness, complications) and c) whether this subgroup of patients will

selectively benefit from antibiotics.

2.3 Previous evidence. Antibiotics and sore throat: A Cochrane review confirms that the risk of complications is five times higher in placebo groups compared with antibiotic treated groups¹¹, but among lower risk groups managed in primary care the incidence of complications is probably only 0.7%¹². The solution is therefore not to increase antibiotic use indiscriminately, but to better identify individuals who are likely to benefit. Here the systematic review does not help clinicians greatly since it does not identify those who are at risk, nor to identify those who will selectively benefit from antibiotics.

Targeting patients who will particularly benefit: Better clinical diagnosis. Currently GPs manage infections empirically, are uncertain about who benefits, and manage their uncertainty by using a range of ad hoc features which they believe predict adverse outcome⁹. The available methods of improving clinical targeting have been systematically reviewed¹³:

Clinical prediction rules. These have perhaps the most promise to be useful in practice since they require no resources and are simple to use^{13 14 15} - the major candidate being the 'Centor' criteria, which predicts the presence of bacteria¹⁰. These criteria were operationalised recently^{16 22} as 3 out of 4 of pus, cervical nodes, a history of fever, and no history of cough.

Is it plausible that clinical prediction rules will predict symptomatic benefit? In all patients in the systematic review there is about 16 hours symptomatic benefit from antibiotics¹¹ and less than a days benefit in unselected patients¹², whereas in the two studies among selected patients with 3 out of the 4 'Centor' criteria 1.5- 2 days benefit was documented^{16;17}. However, this evidence - i.e. that those with the Centor criteria benefit more than those without the criteria - is based solely on historical comparisons.

Is there any evidence that using clinical prediction rules might predict and prevent complications? Using historical comparisons with unselected populations¹², those with the Centor criteria are at least 5 times more likely to develop complications^{16;17}. Provisional evidence from the two studies of antibiotics among those with the Centor criteria^{16;17} - which were underpowered to assess prevention of complications - suggests complications (quinsy, sinusitis, otitis media, cellulitis/impetigo) may be relatively high in the untreated group (3.5%), and prevented in the antibiotics group, although neither trial was powered to assess complications. Thus whilst it is plausible that the Centor criteria predict complications, historical comparisons are unreliable: there have been no adequately powered cohort studies to prove whether the Centor criteria predict complications, nor whether there is selective benefit from antibiotics among those with the Centor criteria. It is also likely that a clinical rule developed specifically to predict complications would perform even better in predicting risk of complications than the Centor Criteria - which were developed to predict the presence of bacteria.

Is there any point developing a rule: would using a clinical rule limit the reduction in antibiotic use? It is not enough to show that patients are at risk, we must show that we can reduce the risk. If we can develop a useful decision rule (this application), we propose a subsequent study to perform a randomised controlled trial to both use and confirm the predictive value of the rule. The approach we will take in the subsequent study will be to advocate antibiotics for the high risk group within 48 hours of seeing the doctor unless their symptoms are starting to settle i.e. using a short 'wait and see' approach. Using a 48 hour wait, there were no complications from 3 studies¹⁸⁻²⁰. We have also used the approach successfully where only 25% used their prescription¹²: Even assuming 50% of those in a high risk group use antibiotics, this will potentially result in only 12% of those attending with sore throat taking antibiotics (i.e. half the high risk group and few or none of the lower risk group)¹². This approach is likely to be highly cost-effective since it will be associated with a significant QALY gain (by avoiding complications, and minimising those with severe or prolonged symptoms) and be cost neutral or cost saving (since the cost of prescribing antibiotics in antibiotic treated groups is balanced by the cost of admission in untreated groups). However there is no point trialling a rule unless it can be shown to be predictive: what is needed first is a study to identify those at risk and develop a decision rule. We are not aware of any study in primary care powered *a priori* to predict those at risk.

3.0 Scientific potential: There is little firm evidence, nor agreement among experts or clinicians about which subgroups do and don't benefit from antibiotics, when rational antibiotic use is a priority. There are two other strategically important areas that this study addresses:

- 1) **Developing methodology.** The methodology - to develop a clinical rule to predict and

prevent complications in a very large cohort - has rarely been achieved in primary care, and will provide a model for the development of similar rules for other RTIs (e.g. LRTI) and other conditions. The methodology will develop:

a) simplified data collection suitable for a high volume, low technology studies; we propose developing both paper and web based version of the data collection tool

b) a novel and highly efficient method of recruiting GPs and nurses to a large study - using collaboration from existing primary care Research Networks, and postal invitation. This study could thus provide a model for recruiting/managing other large primary care cohorts.

2) Clinical research and applying evidence in practice. This study will potentially provide very practical evidence for both health professionals and the general public about who is at risk for one of the commonest clinical problems. Applying this evidence in practice could then potentially make a difference in the management for millions of people. We have chosen a group of lower prescribing practitioners for this study in order to be able to detect complications related to not prescribing antibiotics. However our qualitative work suggests the clinical rule we will develop will apply and be useful to all GPs⁹. In the UK alone the clinical rule can potentially be used in 6 million face to face consultations a year, and a similar number of consultations with NHS direct each year for URTIs - and thus provide an excellent vehicle for the public understanding of science. The study has the potential to maximise benefit to patients who will benefit from antibiotics; minimise harm to patients who will not benefit; minimise the medicalisation of predominantly self limiting illness by cutting antibiotic use further; minimise the risk to public health of antibiotic resistance developing; and provide a clinical rule that is extremely cost effective.

3.1 People and track record. This is a novel collaboration involving 6 departments and local recruiting Networks based in the South West Of England. Each centre will provide local recruiting Networks, and the Birmingham group will provide the web based data system. All the departments meet regularly in regional meetings to present primary care research. Most of the departments have a prior record of interest in respiratory infection research. Each department will have equal status in the management of the study

- Professor Little (current chair of the European General Practice Research Network) with Drs Moore and Williamson are based in the Southampton group and have performed several pragmatic trials of prescribing for respiratory infection (including two trials funded as part of MRC fellowships), and two studies to develop clinical prediction rules. Dr Moore is also director of the Wessex Research Network (WReN) which has a good track record of recruiting large cohorts (for example a 9000 cohort for a randomised trial of vitamin D injections). Mr Mark Mullee is an experienced medical statistician who works closely with the primary care group.
- Professor Mant leads the Oxford Group, and holds an MRC Programme of research into acute childhood infections
- Dr Hay is Senior Lecturer at Bristol University and has won a DOH Post Doctoral Award in the area of decision rules for acute infections.
- Professor Butler leads the Cardiff group and has a high profile track record of both quantitative and qualitative research in respiratory infections
- Professor Campbell leads the Peninsula group whose local GP Network has been instrumental in a number of important studies in acute infections
- Professor Hobbs and Delaney have expertise in clinical decision making, have been instrumental in setting up a secure web based clinical data capture facility based in the Birmingham unit, and have an extensive local GP Network.

3.2 Environment. The study has the support of all the departments of general practice and the support of all local Networks which is essential to ensure this study is successful. Each department also has a close relationship with a successful local research Network of GPs, each of which has existing infrastructure to contact and support members. The Birmingham unit has developed web based clinical data capture. The web based system will correspond to a scannable paper versions of the same forms.

3.3 Research plans.

3.30 Primary objectives: This study will:

- 1) assess whether the Centor criteria predicts common complications (quinsy, otitis media, sinusitis, cellulitis)
- 2) develop a clinical prediction rule to predict a group at high risk of complications

3.31 Summary of study proposed.

Setting. This study is based around high volume simplified data collection, using a cohort of 600 GPs/nurses recruited mainly by postal invitation through existing research Networks at 6 sites.

Methods. Each practitioner will collect data from 30 patients (18,000 patients in total): baseline clinical data will be collected using a structured proforma. Complications or deterioration of illness will be documented from patient records and from patient report.

From this data set we will develop a clinical prediction rule - to predict a group at high risk of complications - and pilot the rule. If a rule is found to be predictive the next step will be a subsequent study (i.e. a separate application) to both confirm the predictive value of the rule in a new data set and trial the use of the rule

Main Outcomes. Suppurative complications (quinsy, otitis media, sinusitis, cellulitis/impetigo). Deterioration in illness. **Other outcomes:** severity/duration of illness.

3.32 Study design: This is a cohort study which will develop a clinical prediction rule, using simple structured clinical proformas - similar to those used in previous smaller studies^{12;21}.

a) Recruitment, feasibility and development of clinical rule, and piloting the clinical rule.

- 0-9 months. Recruit 100 GPs in each centre. We will provide secretarial support provided to existing Networks at each site to recruit GPs and/or nurses (in some practices practice nurses manage URTIs).
 - a) GPs/nurses will be recruited by postal invitation - since data collection of the structured proformas is simplified, it will be very easy to make a decision about participating based on a letter of information and seeing the proforma. For those who are unsure about recruiting based on the postal invitation we will recruit local GP 'champions' to perform visits.
 - b) GPs and nurses will reply to the study centre if they are interested
 - c) The study centre will then send out packs for 30 patients (containing consent forms, patient information leaflets, and paper clinical proformas where the GP prefers not to use the web system). Explanations about how to complete the proformas (e.g. how to use EZTemp™ thermometers, features of history or examination) will be provided on laminated cards as we have used in previous studies in our group²¹, with the study manager as back up by telephone if there are queries. We will recruit low prescribers - otherwise we would not be able to assess complications when antibiotics are not prescribed. Thus we aim to recruit those who prescribe immediate antibiotics less than 50% of the time for sore throat. During first 6 months we will also obtain LReC and clinical governance approval in the various PCTs.
- 4-22 months. Data collection (a minimum of 30 clinical proformas per GP, 18,000 patients in total). The aim is to use simplified baseline clinical data collection in a one page proforma and then subsequently document whether patients developed complications (quinsy, cellulitis, otitis media, sinusitis etc). Recruitment could be completed sooner than 9 months for each practitioner. This gives considerable leeway for any recruitment difficulties since we have allowed 18 months. One in ten (1800) randomly selected patients will also complete a validated symptom diary, however if return rates for diaries are low we may increase the numbers who are randomised to receive a diary.

We will include a small case control study in the Southampton region to further investigate the difference between sore throat patients developing and not developing complications (for both quinsy and patients reporting other complications). A Questionnaire is included with Southampton region packs **not** already containing a diary. Due to the anticipated number of cases of quinsy in this group additional quinsy cases from the CRIS study (antibiotic outreach trial and the Complications of Respiratory Infections Study MREC/02/6/67) will be used and in return DESCARTE will provide extra 'controls' for the CRIS study.

- The patient will have a brief explanation of the study by the GP sufficient to introduce it, and then will be asked by the GP to read the Patient information leaflet. GP practices will also have the option to leave copies of the Patient Information Leaflet in the waiting room (in a display box indicating that patients coming to the Doctor with a sore throat may like to read it). In some practices this may help the process to run more smoothly as the patient will have time to read the information in the waiting room and already have some information about the study before the consultation. The patient will have the opportunity to phone the study centre if they have any queries before completing the consent form. Many patients may be happy to leave copies of the consent form in the practice before they leave (and the GP will send the forms on to the researchers); otherwise patients will send the forms directly to the researchers. The consent forms will be in triplicate so that where the patient leaves the forms in the GP surgery the patient has a copy, the GP has a copy, and the researchers are sent a copy. This will allow the researchers to contact the GP if no consent form is received, without having to bother the patient. The GP will collect the clinical information onto the web or paper clinical proforma (there will be no patient identifiers associated with this data). This has to occur in the consultation otherwise the data will be of very poor quality and will not represent the information we will get in the consultation in routine practice. If the research team do not receive a consent form, it is assumed that the patient has not consented and all the clinical data relating to this patient is deleted from the system.
- 23-30 months. Analysis of predictors of complications from cohort (2 months). We will also develop and pilot clinical decision rule proformas ready for application in a subsequent trial.

3.33 Data management. GPs will have the option of either using paper or web based versions of the proforma - although the web proformas will be our preference

a) Clinical proforma: the proforma will contain no details of patient names or date of birth to minimise confidential data being compromised, but each proforma will have a unique study id number which will identify the practice and the particular patient within each practice.

- Paper clinical proformas. Once each patient is entered into the study, the GP or nurse will send the original copy, and keep a carbon copy.
- Web based proformas. During the first 6 months the web proforma will also be set up on the Birmingham site, accessed by each practitioner using a secure password.

b) Patient identifiers: each patient will also complete a consent form with patient identifiers (patient names, study id number, date of birth, address, phone number and E-mail). There will be 3 copies, one for the researchers, one for the GP and one for the patient. Paper copies of consent form with patient identifiers will be kept physically separate from the clinical proforma files in locked secure cabinets at the study centre. Each of the collaborating centres will require access to consent forms for taking to the GP surgery to perform notes review and to facilitate claiming SFS funding from PCTs (and equivalent body in Wales) on behalf of GPs. This will be made possible by electronically scanning consent forms in Southampton. They will be held in directories at Birmingham University where named administrators from each Centre will, using secure passwords, be able to access the Directory relevant to their Centre to retrieve the necessary information.

The web based system will not require data entry, but the paper forms will be scannable; both paper and web data bases will be compatible so that data can be merged easily.

3.34 Inclusion criteria. Previously well subjects aged 16 years and over with acute illness (14 days or less), presenting with sore throat as the main symptom, with an abnormal examination of the pharynx (identical criteria to our previous studies²²). **Exclusion criteria.** Severe mental problems (e.g. dementia – unable to consent or complete diaries).

3.35 Outcome measures

Outcomes: clinical data, complications, and sociodemographic data will be collected in all patients, but diary and questionnaire information only in 1800 patients.

- **Primary data: clinical proforma.** This will consist of a single clinical sheet documenting baseline clinical data. Study entry will be documented in the notes. We will collect data at presentation on temperature (using EZTemp™ thermometers), the presence and severity of baseline symptoms (sore throat, difficulty swallowing, fever during the illness, runny nose, cough, feeling unwell, diarrhoea, vomiting, headache, muscles ache, abdominal pain, sleep disturbance, earache) on 4 point Likert scales (none, a slight problem, a moderately bad problem, a severe problem), and the presence of signs (pus, nodes, tender nodes,

temperature, inflamed pharynx, inflamed tonsils, palatal oedema, fetor, difficulty speaking) based on previous clinical scores^{10 15 23 16}. The severity of symptoms not simply their presence is probably important: in piloting among 60 patients we have shown that the severity of symptoms rather than the presence of symptoms predicts bacterial infection which we documented by a four fold rise in antibody titres. We will collect information about any antibiotics that were prescribed and any other treatment advice.

- **Complications** (our main outcome). Deterioration of illness (a secondary outcome) has also been used by one of us in a previous cohort of children²⁴ – defined as worsening symptoms sufficient to recontact a health professional, or a new symptom or sign. We will gain information about both complications and deteriorating in illness from two sources:
 - **Patient data.** Patients will be asked to return a FREEPOST card directly to the study centre if they become more unwell, with details, and whether and how they contacted the NHS for help; this will be backed by phone calls for clarification as necessary.
- Notes review:** this will be done independently of the baseline clinical information by a trained clerical assistant in each site. We anticipate on average a deterioration in illness in 1-2 patients and a complication in 0-1 patients per the 30 patient cohort that each GP recruits. We have shown training to perform notes review results in reliable and unbiased assessment in previous studies²². GPs will be asked to document in the notes both deterioration in illness (defined as above) and all cases where there is a complication – a new clinical diagnosis of otitis media, sinusitis, quinsy, and cellulitis documented in the notes within 1 month of the initial presentation. GPs will be asked to document secondary information in each case: quinsy - admission and treatment (i.e.this diagnosis will normally be made by a consultant ENT surgeon following admission and drainage^{6 11}); otitis media - duration of pain, degree of inflammation, evidence of fluid^{21;25}; sinusitis - duration, purulence, lateral prominence of pain or discharge, and 'second sickening' based on clinical prediction rules for sinusitis^{26 27 11} ; cellulitis^{16;17} - diameter of the spreading erythema, systemic upset, any associated impetigo. We will review a randomly chosen selection of verbatim entries into the notes to assess agreement with the documentation performed by the clerical assistants.

Secondary data.

- **Diary scores (among 1800 patients).** The main symptomatic outcome derives from a patient symptom diary (as in previous studies^{12;22}; each symptom is scored 0=no problem to 6=as bad as it could be: sore throat, difficulty swallowing, feeling unwell, fevers, sleep disturbance, cough, tender glands). The main symptomatic outcomes are a) the mean of 2 items, the severity of sore throat and difficulty swallowing during days 2-5 (Cronbach alpha >0.9)), and b) time to resolution of sore throat (total duration; also duration of a moderately bad sore throat). The diary also asks patients to record their own temperature using EZEtemp™ thermometers and documents information about satisfaction with the consultation, enablement, and whether over the counter remedies were used. Patients who receive a diary will be called shortly after they receive their diary to check that they understand what to do and answer any questions they may have. If no diary is received after 2-3 weeks, one mailed reminder will be sent using a brief questionnaire containing the key diary items; if no diary or questionnaire has been returned a brief phone call will clarify the duration and severity of symptoms and whether antibiotics were used; this method has been shown to be both acceptable to patients and allows significantly less bias from low response rates (Little P et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomised controlled trial. JAMA 2005; 293:3029-3035. Little PS et al. An open randomised trial of prescribing strategies for sore throat. B M J 1997; 314:722-727.)
 - **Time.** We will document time taken off work, and until able to do normal activities (i.e. to capture impact for the employed and for the retired, unemployed, and home- makers)
 - **Socio-demographic data.** We will collect demographic data including age, gender, social indices based on post code. This data will be used to document the generaliseability of the sample, and will also be used in the analysis to assess what variables predict adverse outcome (prolonged and severe illness, complications) since these variables are used by some GPs to justify prescribing⁹.
- Selection bias** GPs/nurses will document when eligible patients are, invited to take part in the study, but decline and the reason why. Selection bias and non-response/loss to follow-up bias will be assessed by comparing the socio-demographic/clinical characteristics of those recruited/not recruited and followed up/not followed-up respectively, and by comparing patients

recruited from very high recruiting GPs (those recruiting at the fastest rate) to those from slower recruiting GPs^{22 21}.

3.36 Sample size (all sample size calculations for 5% two-sided significance and 80% power, using the NQuery sample size programme unless stated).

Allowing for clustering. Our studies using structured proformas, or assessing predictors of adverse events (complications, prolonged illness, severe illness) in observational studies from these studies^{12;21;22;28}, suggest that there is no significant clustering of outcome data due to GP or practice when using such a structured approach to clinical measurement. We assume there may be some error in these estimates and there may still be slight clustering at either GP/nurse or practice level (an ICC of 0.01).

Predicting complications. The key sample in this study are those who do not get antibiotics - where we can most easily develop a clinical rule to predict complications. We assume conservatively that:

- any variable, or the resultant clinical score, will predict complications with an OR of 2.5 (ORs of > 5 are likely^{16;17})
- important predictive variables will have a prevalence among those with complications of 35-75%^{12;16;17}
- complications (quinsy, otitis media, cellulitis, sinusitis) occur 1:150 times among unselected patients¹²
- that no more than half of patients received antibiotics⁹

Based on these assumptions then 6749 data forms are needed among those who receive no antibiotics, 13498 considering all patients, or 17,412 allowing for clustering. Allowing for some leeway in these assumptions 30 completed data forms per GP/nurse will provide 18,000 patients in total.

Symptoms. A sample of 1800 patients (900 of whom will not have antibiotics), allowing for 20% loss to follow-up of diaries, will have power to detect variables with prevalences of 20% to 80% with an odds ratio of 2 for adverse symptomatic outcome among the no antibiotic group. Adverse symptomatic outcome is defined as severe symptoms or prolonged symptoms. Assuming each GP or nurse consents 3 patients to complete the diary, this will provide 1800 patients.

Recruitment. The main issue for any study is to tackle recruitment feasibility. This is why we are using very simple 1 page clinical proformas that we have piloted, support from both Network staff and local GP 'champions' where a practice visit is requested, and a rate of recruitment that most GPs and nurses will find easy. Each day a practitioner will have 1-2 patients presenting with sore throat during the autumn and winter months. Thus recruiting 8 patients per month (our planned recruitment rate) - using a proforma that will take a few minutes to complete - should not be difficult. Even if recruitment is at a half this rate the study will still achieve its target.

Are there likely to be any problems with compliance? We have found no difficulty in a small pilot study (of 60 patients) nor into previous studies using structured proformas^{12;21;29}. The proformas are easier than those we have used before - since there is no randomisation. For the few patients completing diaries, the main symptomatic outcome is acceptable and has already been validated and piloted. Most patients will not be asked to do anything other than having their notes reviewed - which should make recruiting patients very easy.

Loss to follow-up. Based on current studies we anticipate 98% follow-up for notes review. The recruitment figures are based on receiving 30 completed forms from each GP.

Recruitment. Recruitment will be co-ordinated through the 6 local networks.

Data analysis, and subgroup analysis using SPSS and STATA for windows.

Main analysis: observational data. We will assess the predictors of complications using logistic regression, and the predictors of symptomatic outcomes using multiple regression. We will develop a rule a) preferably based on the simple count of predictive variables (like the Centor criteria) which will be the simplest to use in clinical practice, but we will also explore the possibility of using b) a weighted rule (where each variable is weighted according to the rounded logistic coefficients). We will develop similar rules to predict i) the deterioration in illness and ii) for those with severe symptoms (above the median diary score) during the few days after seeing the doctor

3.37 Pilot study. We have piloted the clinical forms among 60 patients. Although the study is very simple and should work well based on our piloting it will rapidly become apparent if the study as proposed is feasible. We propose that the funds for the remaining time are only released

subject to satisfactory recruitment during the first year.

3.38 NHS cost implications for this study. We will apply to NHS R+D for the NHS cost implications for this study – for time to explain the study (service support), to perform the clinical assessment that might be used in practice (service support), and notes access (service support). (Also see discussion of 'grey' areas below)

3.39 Timecourse: 30 months. 0-6 months: recruit GPs, pilot data collection, and gain PCT research governance approval; 4- 22 months: continue to recruit and retain GPs and data collection; 23-30 months data cleaning, analysis, write up, and piloting clinical decision rule. We anticipate that this time course will allow completion of the project. However, if data collection is much slower than anticipated, once the data collection systems are set up a no cost extension of the grant can be requested and data collection can still proceed in two subsequent winters.

4. Resources: Costs are needed for a study manager to run the study, and a 0.5 WTE secretary to manage the data base, additional secretarial support to make up the initial packs. A P/T clerical assistant is needed in each site for 22 months to support the existing Networks in recruiting and maintaining GP recruitment by post (0.4 wte), supported by local GP 'champions' in each centre who will visit the minority of practices who are likely to request visits. A full time clerical assistant is needed in each site to perform notes review. A computer is needed at each site, and one for the study data base manager ; data entry package and support, travel, stationery, postage and telephone, and research costs of GP and/or nurse involvement in each practice to cover the time completing data forms.

Arguably much of the cost of notes review could be provided by support for science – and there are precedents for this. However, since this is a key outcome and since this a 'grey' area, we have provisionally included a staff element for notes review under research costs, but also with a contribution from support for science. Similarly the GP or nurse time assessing patients for a clinical scoring method is arguably almost all service support costs. If after negotiation with the Department of Health, both these grey areas we have identified can be covered fully by support for science, the cost to the MRC will be less.

5. Ethical and Other Implications: There are no significant ethical issues in this study since the behaviour of GPs will simply be observed, i.e. we will not intervene. Confidentiality of personal data will be maintained by separating personal information from the clinical data, and by only allowing access to the web based forms based on secure passwords for each GP. We will obtain MReC approval for the work, and in each PCT research governance approval will be needed before the work could start.

6. Public Engagement in Science : Given that most people experience a sore throat during the winter months each year, and 10%-20% of the population see their GP with a sore throat each year or contact NHS direct, the potential to engage the public with the results of this study addressing such an everyday clinical issue are considerable. We will communicate information about our work to the lay public via the local and national media.

7. Exploitation and Dissemination: It is unlikely that the proposed research will generate commercially exploitable results. If a clinical rule can be developed which can be proven to reduce complications this will be key data for general practice and is likely to have a major impact in practice. These results will be presented at local and national academic meetings, to local post-graduate and undergraduate meetings for family physicians, to MeReC, to the DTB, to the GPs magazines (Pulse, Doctor etc).

8.0 Application history. A smaller blinded explanatory efficacy trial with intensive microbiological investigation to assess symptomatic benefit from using a clinical rule was potentially felt to be alpha A, and the Board deferred a decision. After deferring the decision, the Board felt that the study would not change practice unless a study also dealt with complications – and the study was not recommended for funding. This is a completely different methodology, a different study addressing different hypotheses – but particularly addressing the issue of complications - and is the first submission of this application.

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