Appendix D: Clinical evidence tables

Study	Aabenhus 2014[3] Cochrane review
Study type	Systematic review – effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers.
Number of studies (number of participants)	Six RCTs (3284 participants; 139 children).
Countries and setting	Russia, the Netherlands, Denmark, Spain, England, Wales, Poland, Belgium and Norway.
Duration of study	Databases were searched for papers published during the following time periods: CENTRAL (2013, Issue 12), MEDLINE (1946 to January 2014), EMBASE (2010 to January 2014), CINAHL (1981 to January 2014), Web of Science (1955 to January 2014) and LILACS (1982 to January 2014).
Stratum	-
Subgroup analysis within study	N/A.
Inclusion criteria	Randomised controlled trials (RCTs) in primary care patients with acute respiratory infections (ARI) that compared use of point-of-care biomarkers with standard of care. Trials that randomised individual patients as well as trials that randomised clusters of patients (cluster-RCTs) were included.
Exclusion criteria	Studies in which the analysis was not performed at the point-of-care, studies not conducted in a primary care setting and studies used a before-and-after design.
Recruitment/selection of patients	Primary care patients of all ages with symptoms from, or a diagnosis of, an ARI at study entry. Symptoms of ARI were defined as cough, discoloured/increased sputum, fever, runny nose, respiratory distress, feeling unwell, or combinations of focal and systemic symptoms having a duration of less than 4 weeks. Diagnoses included lower or upper respiratory tract infection, pneumonia, bronchitis, acute exacerbations of chronic obstructive pulmonary disease or asthma, pharyngitis, tonsillitis, laryngitis, rhinosinusitis, common cold, acute otitis media or influenza.
Age, gender and ethnicity	Age (mean, SD) intervention group: 45.3 (16.8), control group: 46.0 (17.2); % female intervention group: 62.8 control group: 64.3; ethnicity: not reported.

Study	Aabenhus 2014[3] Cochrane review
Further population details	Patients with acute respiratory infections (ARI).
Extra comments	Types of studies included in this review: 1. Patient or cluster randomised controlled trials (RCTs). 2. Patient or cluster controlled clinical trials (CCTs).
Indirectness of population	No indirectness.
Interventions	Biomarkers of infection act as surrogate measures of the immune response to infection and may reflect the severity of the condition A point-of-care test exists for some of these biomarkers to be performed at, or near, the site of patient care, delivering quick test results that can influence clinical decisions. The decision to prescribe antibiotics for an ARI is guided by pre-specified cut-off values specific to the individual point-of-care test but the test cannot replace clinical skills and expertise, and test results may be overruled on clinical grounds.
Funding	Not stated.

Study	Burri 2012[10]
Study type	RCT (Patient randomised; Parallel).
Number of studies (number of participants)	1 (n=323).
Countries and setting	Conducted in Switzerland; setting: the study was conducted by 29 primary care physicians in Switzerland and Germany and was co-ordinated at the University Hospital Basel, Switzerland. Sites were selected on the basis that patients could directly present to primary care physicians as a first point of consultation. Thus, the participating physicians represented a range of medical backgrounds from GPs to physicians with additional training in internal medicine, pneumology and cardiology. Participating practices were equally distributed in urban and suburban areas.
Line of therapy	1st line.
Duration of study	Intervention + follow up: point of care testing plus 12 months follow up.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis.
Stratum	Overall.

Subgroup analysis within study	Not applicable.
Inclusion criteria	Eligible patients presented with dyspnoea as their primary symptom. This had to be of new onset or clearly worsening if pre-existing. If multiple symptoms were present in an individual patient, dyspnoea had to be the main symptom.
Exclusion criteria	Patients younger than 18 years of age or with an obvious traumatic cause of dyspnoea, severe renal disease (serum creatinine level of more than 250 micromol/L) or sepsis were excluded.
Recruitment/selection of patients	323 consecutive patients were enrolled.
Age, gender and ethnicity	Age - Median (IQR): Intervention group: 73 (64-80), control group: 71 (62-79). Gender (M:F): Intervention group: 53% female, control group: 55% female. Ethnicity: not reported.
Further population details	-
Indirectness of population	No indirectness.
Interventions	(n=163) Intervention 1: GP access to laboratory investigations within practice hours - GP access to phlebotomy and blood tests with same day results within practice hours including cardiac biomarkers which included BNP and/or CRP and/or renal function and/or, full blood count and/or LFT. Rapid point-of-care testing measurement of BNP at initial presentation. 3ml of venous blood was collected into a potassium EDTA tube. Within a 15 minute period, BNP was measured using a rapid fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). The same assay was used at all participating centres. All physicians were repeatedly trained in the most appropriate use of BNP levels in this indication. B-type natriuretic peptide was considered a quantitative marker of cardiac stress and heart failure. In the absence of BNP cut-off levels validated specifically inpatients presenting with dyspnoea to primary care physicians, we applied the cut-off levels validated inpatients presenting with acute dyspnoea to the ED. This decision was further supported by a large study performed in the primary care setting that demonstrated a comparable optimal cut-off level of NT-proB-NP as previously reported in studies conducted in the ED. Two cut-off levels of BNP to separate dyspnoea caused by heart failure from other causes of dyspnoea were suggested. In patients with a level below100 ng L)1, the diagnosis of heart failure was considered unlikely and alternative causes of dyspnoea had to be investigated. In patients with a BNP level above 400 ng L)1, heart failure was considered the most likely diagnosis and therapy with diuretics, nitro-glycerine, angiotensin-converting enzyme inhibitors (slow up-titration), beta blockers (slow up-titration) and spironolactone was recommended. BNP levels between 100 and 400 ng L)1 suggested the presence of mild heart failure, but clinical judgment and further diagnostic testing were recommended to exclude pulmonary embolism. Adjustments were recommended in patients with renal dysfunction and obesity (higher and lower cut-off levels, respectively). Duration: 12 months follow-up. Concurrent medication/care: all patients underwent an initial clinical assessment that, in general, included a clinical history, physical examination and electrocardiography. Chest radiography and pulmonary function tests were performed based on clinical decision. Diagnostic and therapeutic decisions were not based on BNP levels alone, instead this information was considered in the context of other clinical information obtained and the physician's clinical opinion.

	(n=160) Intervention 2: No GP access to laboratory investigations. Evaluation using the conventional diagnostic strategy without the measurement of BNP. Patients in the control group were evaluated and treated according to the most recent clinical guidelines. Duration: 12 months follow up. Concurrent medication/care: all patients underwent an initial clinical assessment that in general included a clinical history, physical examination and electrocardiography. Chest radiography and pulmonary function tests were performed based on clinical decision.
Funding	Equipment/drugs provided by industry (ALERE provided the rapid fluorescence immunoassay for the point of care measurement of BNP).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GP ACCESS TO PHLEBOTOMY AND BLOOD TESTS WITH SAME DAY RESULTS WITHIN PRACTICE HOURS INCLUDING CARDIAC BIOMARKERS INCLUDING BNP AND/OR, CRP AND/OR RENAL FUNCTION AND/OR, FULL BLOOD COUNT AND/OR LFT versus NO GP ACCESS TO LABORATORY INVESTIGATIONS. Protocol outcome 1: Laboratory or diagnostic turnaround or result to GP. - Actual outcome: Time to appropriate therapy at days; Group 1: mean 12.8 days (SD 31.3); n=163, Group 2: mean 24.7 days (SD 41.3); n=160; Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: ED attendance - Actual outcome: Hospitalisations after 3 months at 3 months; Group 1: 28/163, Group 2: 20/160; Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness - Actual outcome: Hospitalisations after 12 months at 12 months; Group 1: 50/163, Group 2: 42/160; Risk of bias: low; ; Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - - Low; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life; Antibiotic usage; Avoidable adverse events; Patient and/or carer satisfaction.

Study	**Cals 2009[14]**
Study type	RCT (GP surgeries/practices randomised; Parallel).
Number of studies (number of participants)	1 (n=431).
Countries and setting	Conducted in Netherlands; setting: 40 general practitioners based in 20 general practices in the Netherlands.
Line of therapy	1st line.
Duration of study	Intervention + follow up: 10 weeks.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	Suspected lower respiratory tract infection with a cough lasting less than 4 weeks together with 1 focal and 1 systemic symptom.
Exclusion criteria	None reported.
Recruitment/selection of patients	Sequential eligible adults with regular consultation hours during the winters of 2005-6 and 2006-7.
Age, gender and ethnicity	Age - Mean (SD): CRP test group: 49.4 (14.7), control group: 50.3 (16.0). Gender (M:F): CRP test group: 59%, control group: 64.2%. Ethnicity: not reported.
Further population details	-
Indirectness of population	No indirectness.
Interventions	(n=227) Intervention 1: GP access to laboratory investigations within practice hours - GP access to phlebotomy and blood tests with same day results within practice hours including cardiac biomarkers including BNP and/or CRP and/or renal function and/or, full blood count and/or LFT. Clinicians were given devices to test for CRP (NycoCard II Reader, Axis Shield, Norway) according to the manufacturer's instructions. A result can be available within 3 minutes, using a drop of blood obtained by finger prick. GPs were given guidance on how to use the test results within the consultation during a 30 minute practice based training session delivered by the study team. The additional value of C reactive protein in ruling out serious infection was emphasised. An 8 week run-in period enabled familiarisation with the devices before patient recruitment. Duration: 10 week follow up. Concurrent medication/care: n/a. (n=204) Intervention 2: No GP access to laboratory investigations. Usual care with no CRP testing. The Dutch guideline for managing acute cough, including diagnostic and therapeutic advice for lower respiratory tract infection, is distributed to all GPs in the Netherlands and informs usual care. Duration: 10 week follow-up. Concurrent medication/care: n/a.

Funding	Academic or government funding (Netherlands Organisation for Health Research and Development).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GP ACCESS TO PHLEBOTOMY AND BLOOD TESTS WITH SAME DAY RESULTS WITHIN PRACTICE HOURS INCLUDING CARDIAC BIOMARKERS INCLUDING BNP AND/OR,CRP AND/OR RENAL FUNCTION AND/OR, FULL BLOOD COUNT AND/OR LFT versus NO GP ACCESS TO LABORATORY INVESTIGATIONS. Protocol outcome 1: Patient satisfaction. - Actual outcome: Patients very satisfied and above at NR; Group 1: 159/227, Group 2: 76/204; Risk of bias: All domain - high, Selection - Low, Blinding - high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no serious indirectness Protocol outcome 2: Antibiotic usage. - Actual outcome: Antibiotic prescription at first appointment at first appointment; Group 1: 70/227, Group 2: 108/204; Risk of bias: All domain - high, Selection - Low, Blinding - high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no serious indirectness - Actual outcome: Antibiotic prescribing within 28 days of first appointment at 28 days; Group 1: 102/227, Group 2: 119/204; Risk of bias: All domain - high, Selection - Low, Blinding - high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no serious indirectness	
Protocol outcomes not reported by the study	Quality of life; ED attendance; Avoidable adverse events; Laboratory or diagnostic turnaround or result to GP.

Study	**Dahler-Eriksen 1999[21]**
Study type	RCT (GP surgeries/practices randomised; Parallel).
Number of studies (number of participants)	1 (n=1853).
Countries and setting	Conducted in Denmark; setting: 41 GP clinics in the catchment area of Vejle County Central (Denmark) hospital lab were invited to participate in the study. 29 clinics accepted. The clinics were randomised into 1 of 2 groups and after 3 months the 2 groups interchanged (crossover). The first period of intervention and control was 3 months April-June 1996 and the second period was 4 months (July-October 1996).
Line of therapy	1st line.
Duration of study	Intervention time.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	Not reported.
Exclusion criteria	Incomplete registration of personal registration numbers.
Recruitment/selection of patients	The GP filled out a registration card for each patient when a CRP was measured or ordered.
Age, gender and ethnicity	Age - Other: mean: 53.7 CIs: 52.8-54.6. Gender (M:F): 60.2% women (CI 58.0-62.4). Ethnicity: not reported.
Further population details	-
Indirectness of population	No indirectness.
Interventions	(n=919) Intervention 1: GP access to laboratory investigations within practice hours - GP access to phlebotomy and blood tests with same day results within practice hours including cardiac biomarkers which included BNP and/or CRP and/or renal function and/or, full blood count and/or LFT. GP had access to a near-patient test for CRP (NycoCard CRP whole blood, Nycomed Pharma) in the office. Duration n/a. Concurrent medication/care: no clinical guidelines for the use of CRP were distributed to the clinics. (n=934) Intervention 2: Standard services - as defined in study. CRP had to be ordered as usual, by mailing a blood sample to the laboratory. Duration not reported. Concurrent medication/care: no clinical guidelines for the use of CRP were distributed to the clinics.
Funding	Academic or government funding (Danish Medical Research Council).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GP ACCESS TO PHLEBOTOMY AND BLOOD TESTS WITH SAME DAY RESULTS WITHIN PRACTICE HOURS INCLUDING CARDIAC BIOMARKERS INCLUDING BNP AND/OR,CRP AND/OR RENAL FUNCTION AND/OR, FULL BLOOD COUNT AND/OR LFT versus AS DEFINED IN STUDY. Protocol outcome 1: Antibiotic usage - Actual outcome: Antibiotics prescribed; Group 1: 168/529, Group 2: 154/472; Comments: Patients with infection as the tentative diagnosis and with unspecific diagnoses such as fever, cough or dyspnea are included in this analysis. Patients in a follow-up course and with appendicitis were excluded Risk of bias: All domain - high, selection- high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Intervention group purpose of CRP test was likely to be diagnosis of new disease, control group purpose of CRP test was likely to be follow-up	
Protocol outcomes not reported by the study	Quality of life; Laboratory or diagnostic turnaround or result to GP; ED attendance; Avoidable adverse events; Patient and/or carer satisfaction.