EUnetHTA Joint Action 3 2016-2020

C-reactive protein point-of-care testing (CRP POCT) to guide antibiotic prescribing in primary care settings for acute respiratory tract infections (RTIs)

Project ID: ***OTCA12***

Project description and planning

Health Information and Quality Authority An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte	Hauptverband der österreichischen Sozialversicherungsträger
Ireland	Austria

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Version Log

Version number	Date	Modification	Reason for the modification
V1.0	19/02/18	First draft	First draft
V2	14/03/18	Second draft	Amendments subsequent to comments from dedicated reviewers. Editorial changes to improve consistency and clarity of language.
V3	13/04/2018	Final draft	Amendments subsequent to comments from external experts, patient representative and assessment meeting scoping team

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1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Health Information and Quality Authority - HIQA	Author	Ireland	• Develop the first draft of the EUnetHTA project plan. • Perform the literature search and study selection. • Undertake the assessment (data extraction, analysis, synthesis, and interpretation of findings). • Lead on the writing of the draft report. • Circulate draft report to dedicated reviewers and external experts, compile and respond to feedback, and edit draft report, as appropriate. • Send final document to manufacturers for fact check. • Prepare final assessment and write the final summary of the assessment.
2.	Hauptverband der österreichischen Sozialversicherungsträger (HVB)	Co-Author	Austria	• Collaboration in the development of the EUnetHTA project plan • Check, provide input and endorse all steps (e.g. collaboration in literature selection, data extraction, assessment of risk of bias). • Check, provide input and endorse content of all domains. Collaborate on the writing of the discussion and conclusions, and endorse same. • Review drafts of the assessment, propose amendments where necessary and provide written feedback.
3.	Healthcare Improvement Scotland (HIS)	Dedicated Reviewer	Scotland	• Review draft project plan, propose amendments where necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method). • Review assessments, propose amendments where necessary and provide written feedback.
4.	Università Cattolica del Sacro Cuore (UCSC) Gemelli	Dedicated Reviewer	Italy	• Review draft project plan, propose amendments where necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method). • Review assessments, propose amendments where necessary and provide written feedback.
5.	Agencia de Evaluación de	Dedicated	Spain	• Review draft project plan, propose

	Tecnologías Sanitarias de Andalucía (AETSA)	Reviewer		amendments where necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method). • Review assessments, propose amendments where necessary and provide written feedback.
6.	AGENAS - Agenzia Nazionale per i Servizi Sanitari Regionali (AGENAS)	Dedicated Reviewer	Italy	• Review draft project plan, propose amendments where necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method). • Review assessments, propose amendments where necessary and provide written feedback.
7.	Agency for Health Technology Assessment and Tariff System (AOTMiT)	Observer	Poland	• Review draft project plan, propose amendments where necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method). • Review assessments, propose amendments where necessary and provide written feedback.
Contributors				
8.	Elizabeth Beech, National Project Lead - Healthcare Acquired Infection and Antimicrobial Resistance, NHS Improvement	External Expert	England	• Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; • Review methods, results, and conclusions based on the original studies included; • Provide constructive comments in all the project phases
9.	Dr Nuala O'Connor, Irish College of General Practitioners (ICGP) GP Lead HSE Clinical Programme HCAI-AMR	External Expert	Ireland	• Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; • Review methods, results, and conclusions based on the original studies included; • Provide constructive comments in all the project phases
10.	Professor Martin Cormican, National Clinical Lead for HCAI and AMR; Consultant Microbiologist; Professor of Bacteriology, National University of Ireland, Galway.	External Expert	Ireland	• Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; • Review methods, results, and conclusions based on the original studies included; • Provide constructive comments in all the project phases
11.		Medical Editor		
12.	Health Information and Quality Authority (HIQA)	Project Manager	Ireland	• Project management

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	Role in the project
Abbott (formerly Alere)	Manufacturer
Biosurfit	Manufacturer
Boditech Med	Manufacturer
DiaSys Diagnostic Systems GmbH	Manufacturer
Eurolyser Diagnostica	Manufacturer
Horiba	Manufacturer
Medix Biochemica	Manufacturer
Orion Diagnostica Oy	Manufacturer
Radiometer Medical ApS	Manufacturer
Servoprax	Manufacturer
RPS Diagnostics	Manufacturer
Patient Focus (Ireland)	Patient representative

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**29/01/2018**	**10/09/2018**
Scoping phase	**29/01/2018**	**17/04/2018**
Identification of manufacturer(s) and external experts; *optional: identification of patients*	12/02/2018	16/02/2018
Scoping and development of draft Project Plan incl. preliminary PICO	19/02/2018	23/02/2018
Share the preliminary PICO with external experts *(and patients)* for comments		
Send the preliminary PICO for comments (in case there is no scoping meeting planned) *and the request for the completion of the Submission file template to manufacturer(s) (optional)*	01/03/2018	07/03/2018
Consultation of draft Project Plan with dedicated reviewers	28/02/2018	07//03/2018
Consultation of draft Project Plan with external experts *(and patients)* and fact check by manufacturers	15/03/2018	12/04/2018
Internal Scoping e-meeting with the assessment team	29/03/2018	
Amendment of draft Project Plan & final Project Plan available	29/03/2018	17/04/2018
Completion of Submission file template by manufacturer(s) + Clarifying further questions concerning draft Submission file) (optional)	02/03/2018	27/04/2018
Assessment phase	18/04/2018	28/09/2018
Writing first draft rapid assessment	16/04/2018	27/05/2018
Review by dedicated reviewer(s)	28/05/2018	10/06/2018
Writing second draft rapid assessment	11/06/2018	01/07/2018
Review by ≥ 2 external clinical experts and fact check by manufacturers	02/07/2018	22/07/2018
Writing third draft rapid assessment	23/07/2018	12/08/2018
Medical editing	13/08/2018	26/09/2018
Writing of fourth version of rapid assessment	27/09/2018	26/09/2018
Formatting	27/09/2018	28/09/2018
Final version of rapid assessment		**Week of 28/09/2018**

2 Project outline

2.1 Project objectives

The rationale of Work Package 4 is to collaboratively produce structured (rapid) core HTA information on other technologies. In addition, the aim is to apply those collaboratively produced assessments in the national or regional context.

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1	To jointly produce HTAs that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies.	Production of 1 (rapid) relative effectiveness assessment.
2	To apply this collaboratively produced assessment into local (e.g. regional or national) context.	Production of ≥2 local (e.g. national or regional) reports based on the jointly produced assessment.
3	To determine the effectiveness and safety of C-reactive protein POCT in guiding antibiotic prescribing for patients presenting with symptoms of acute respiratory tract infections (RTIs) in primary care.	Production of a rapid assessment according to the research questions outlined in Tables 2-5 a, b and c.

This rapid assessment addresses three research questions in relation to the use of C-reactive protein point-of-care testing (POCT) to guide antibiotic prescribing in patients presenting with symptoms of acute respiratory tract infection (RTI) in primary care settings:

Does the use of C-reactive protein POCT lead to a significant reduction in antibiotic prescribing without compromising patient safety?

What is the diagnostic test accuracy of C-reactive protein POCT devices?

Do the commercially available CE-marked C-reactive protein point-of-care tests have comparable analytical performance?

2.2 Project method and scope

2.2.1 Approach and method

Table 2-2: Project approach and method

Project approach and method
For all domains the selection of assessment elements will be based on the HTA Core Model For Rapid Relative Effectiveness Assessments version 4.2. **Description and technical characteristics of technology (TEC) and health problem and current use (CUR) domains** Antimicrobial resistance is a growing and significant threat to public health, and it is widely recognised that antibiotic resistance is driven by excessive and inappropriate antibiotic prescribing.[1, 2] A number of ecological studies have shown that increased antibiotic consumption correlates with increased antibiotic resistance, with countries that have moderate to high consumption of antibiotics also having high antimicrobial resistance (for Europe these countries tend to be in the south and east of Europe).[2] At the patient level, there is a clear link between

antibiotic dose and duration and the emergence of antibiotic resistance, and there is also evidence that patients who have been treated frequently with antibiotics are at greater risk of antibiotic resistance.[2, 3] The consequence of antimicrobial resistance is increased mortality and morbidity from bacterial infections as well as an increased economic burden on the healthcare sector in the treatment and care of patients infected with multidrug resistant strains as well as a loss of productivity.[4] The societal costs in Europe of selected antibiotic resistant bacteria were estimated to be about €1.5 billion a year in 2007.[5]

Although it is not yet clear how much of a reduction in use would be required to have a beneficial effect on resistance, the clear link between antibiotic prescribing and antimicrobial resistance has led to the promotion of rational use of antibiotics with the ultimate goal of decreasing the consumption of antibiotics within the country without increasing mortality or morbidity. Currently, most antibiotics are prescribed in primary care, frequently for acute respiratory tract infections (RTIs). Acute RTIs include upper and lower respiratory tract infections, pneumonia, bronchitis, pharyngitis, tonsillitis, laryngitis, rhinosinusitis, otitis media, the common cold and influenza. While most of these RTIs are viral, a small number are caused by bacteria and may respond to antibiotic therapy.[6, 7] Guidelines in the UK recommend the use of antibiotics to treat RTIs such as bacterial pneumonia,[8] but there is limited evidence to support the use of antibiotics in acute bronchitis, sore throat (pharyngitis) or otitis media and, in many cases, the use of antibiotics will not be beneficial to the patient's recovery and will expose them to potential side effects of antibiotic treatment.[9-12] It is not possible to determine if a respiratory infection is bacterial or viral based solely on presenting symptoms.[13, 14] Where there is clinical uncertainty regarding the need for an antibiotic, the use of 'delayed' prescriptions (where the doctor prescribes an antibiotic, but asks the patient to wait a few days and only redeem the prescription if the symptoms do not improve or become worse) has been shown to be an effective strategy in reducing antibiotic use. [15]

There are a number of biomarkers that are helpful in differentiating between bacterial and viral infections. C-reactive protein (CRP) is one of these biomarkers and is available as a point-of-care test suitable for use in primary care.[16] C-reactive protein forms part of the immune response and is activated following tissue injury due to infectious and non-infectious conditions such as inflammation and trauma. Levels are typically low in healthy people (<20mg/litre), but increase rapidly during inflammation and tissue damage.[17, 18] They remain high until tissue damage stops and then rapidly decline. The objective of C-reactive protein POCT is to rule out serious bacterial infections, thereby supporting a decision not to provide an antibiotic to those who are unlikely to benefit from treatment and to identify those patients who are most likely to benefit from an antibiotic. The test can produce false positive as well as false negative results leading to the possibility of over or under treatment of RTIs.[16] Over treatment can lead to avoidable adverse reactions to antibiotics and in those who are under treated there is the potential to increase morbidity or mortality.

A number of CE marked C-reactive protein point-of care tests are commercially available. Most are quantitative and require a small amount of whole blood, plasma or serum, with samples combined with appropriate reagents using a test kit. For quantitative methods, a desktop analyser is then used to measure the assay results with the results being expressed in mg/litre with guidelines recommending treatment with antibiotics above a certain level. For example, the UK NICE guidelines for diagnosis and management of pneumonia in adults, recommends CRP POCT should only be considered for people with symptoms of a lower RTI if the diagnosis is unclear after clinical assessment. The guideline recommends not routinely offering antibiotic therapy to those with a CRP <20 mg/L, to consider a delayed prescription in those with a CRP between 20 and 100 mg/L and to offer antibiotic therapy to those with a CRP >100 mg/L.[8]

Most of the CRP point-of-care analyser devices are small and do not require a large amount of

training to use them. In addition, depending on the device, they often can be used for other assays in addition to C-reactive protein, for example, immunochemical faecal occult blood tests, urine albumin, HbA1c, urine albumin/creatinine ratio, D-dimer levels, lipoprotein A, total leucocytes, white blood cells, haematocrit and haemoglobin. Semi quantitative methods for measuring C-reactive protein are also available as point-of-care tests. These involve the use of a small amount of blood, plasma or serum, but they do not require an analyser. These tests provide the user with an indication of whether the patient has low, medium or high C-reactive protein levels. In some cases the C-reactive protein test is used in combination with another biomarker to increase the sensitivity or specificity of the test. For example, a semi-quantitative CRP method, FebriDx, uses CRP in combination with myovirus resistance protein A (MxA) (a non-specific protein marker that is raised in the blood in the presence of an acute viral infection) and the combination of these two biomarkers assists in the differentiation between bacterial and viral aetiology where there is clinical uncertainty.[19]

Debate over the accuracy of point-of-care tests and their effect on antibiotic prescribing is ongoing. Some studies have found the analytical performance of the POCT comparable to laboratory testing, while others have reported that certain pieces of equipment are more accurate and precise than others.[20, 21] The ability of CRP POCT to aid in the diagnosis of serious bacterial RTIs is unclear with some studies finding it useful in primary care,[22] while others have reported it to have limited utility.[23] The subsequent effect of CRP POCT on the prescription of antibiotics has shown conflicting results, with some studies finding it significantly reduces antibiotic prescribing,[16, 24] while others have found it has little effect [18, 22] or may even lead to an increase in antibiotic use[25] and in hospitalisation rates.[16]

- Table 1-2 lists the known manufacturers of this technology. Input from the manufacturers regarding the technical characteristics, price, marketing, current use and availability of products within different countries will be sought. The short version of the EUnetHTA submission file will be used as a starting point to collect these data.
- Input from clinical experts on the best available epidemiological data, current use of the technology and current standard care for the patient group will be sought.
- Use of C-reactive protein POCT in conjunction with communication training has been shown to be more effective at reducing antibiotic use than the use of C-reactive protein POCT on its own.[26, 27] This will be further explored in the systematic searches performed for the clinical effectiveness and safety domains.
- Clinical guidelines. The use of C-reactive protein POCT is currently recommended in a number of guidelines throughout Europe.[8, 28-30] Guidelines will be searched and appropriate information on current recommendations as well as citations of epidemiological data will be extracted.

Clinical effectiveness (EFF) and safety (SAF) domains

Systematic searches

To identify relevant studies, systematic searches will be carried out in the following databases:

- MEDLINE, Embase, The Cochrane Library, (CINAHL via EBSCOHost)
- Ad hoc internet searches to identify relevant grey literature including relevant health technology assessments (HTAs)
- Reference list of included studies and relevant systematic reviews.

All titles and abstracts retrieved by electronic searching will be downloaded to a reference manager (EndNote X7) and duplicates will be removed. Two reviewers will screen citations and full texts of any potentially eligible studies will be obtained. Reasons for exclusion of full text articles will be recorded. Where consensus on study eligibility cannot be agreed based on the pre-defined inclusion exclusion criteria, a third reviewer will be involved. Any additional studies obtained from

systematic reviews, health technology assessments (HTAs) and hand searching of the reference lists of included studies will be added to the database. Data extraction and quality assessment/risk of bias assessment using standardised data extraction forms will be performed independently by two people, with any disagreements being resolved by discussion or a third reviewer.

Systematic review 1: To assess the efficacy, effectiveness and safety of C-reactive protein POCT in reducing antibiotic prescribing, relevant randomised controlled trials (RCTs), cluster RCTs, non-randomised trials and observational studies will be identified. Studies will be excluded if they are not conducted in a primary care setting or if C-reactive protein testing is not performed at the point of care. RCTs and observational studies will be analysed separately and appropriate subgroup analysis (e.g., grouped based on type of RCT, cluster or individual randomisation) will be performed. Where data permit, the following subgroup analyses are planned: upper versus lower respiratory tract infections; children versus adults; older adults (≥ 65 years) versus younger adults (<65 years); by treatment setting (out-of-hours or long term care settings); and by CRP cut-point. Safety outcomes including adverse drug reactions, need for reconsultation or hospitalisation will also be extracted from the studies where available.

As it is currently unclear the extent to which the commercially available C-reactive protein POCT are interchangeable, a review of the evidence regarding the diagnostic test accuracy and analytical performance of the available products is necessary to inform any decision around the product(s) that could be used in the event that there is evidence that use of CRP POCT to guide antibiotic prescribing is safer and or more effective than current care

Systematic review 2: This systematic review will include studies that assess the diagnostic utility of CRP POCT against the current gold standard (microbiological/laboratory/radiological confirmation). The gold standard will be determined by the RTI (e.g., pneumonia, pharyngitis), and different RTIs will be analysed separately. If sufficient data are available, a subgroup analysis will be performed based on CRP cut-points, device type and age of population.

Systematic review 3: The analytical performance of the individual CRP POCT devices will be sought as this information will be useful in determining to what extent the commercially available products are interchangeable. Measures of accuracy (level of agreement between the result of one measurement and the true value) and precision (degree of reproducibility of the result) will be extracted for each CRP POCT. Where available, information on ease of use and suitability for primary care POCT will also be collected and summarised for each device.

As noted, the short version of the EUnetHTA submission file (Medical Devices Evidence Submission template)[31] will be sent to all relevant manufacturers of the technology under assessment. Manufacturers will be asked to submit non-confidential evidence, focusing on the technical characteristics and current use of the technology as well as any non-published studies of the analytical performance of the product. The evidence provided will be used in addition to the literature identified by the literature search.

Assessment of methodological quality of included studies

Assessment of methodological quality of included studies will be performed by the author (HIQA) and checked by the co-author (HVB), with disagreements being resolved by discussion. For RCTs the methodological quality will be assessed using the Cochrane tool for assessing the risk of bias in randomised trials.[32] For observational studies, elements from the Newcastle- Ottawa Scale (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) will be used to assess the risk of bias. Assessment of risk of bias in DTAs will be assessed using QUADAS 2.

The quality of the body of evidence will be assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). Experts, patient representatives (if available), authoring and reviewing teams will be involved in grading the importance of each of the outcomes identified. The summary of findings table will be created using the GRADE PRO tool. Relevant subgroup analyses will be assessed especially for the most important outcomes. Evidence from observational studies will by default be rated as low, but the quality can be upgraded based on: 1) a strong or very strong association, 2) a dose-effect relationship, 3) if all plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed.

Table 2-3: Planned literature search strategy

Literature search strategy
Three systematic reviews will be undertaken: • A systematic review on the use of C-reactive protein POCT to guide antibiotic prescribing in patients presenting with symptoms of acute respiratory infections in primary care settings. • A systematic review on the diagnostic test accuracy of C-reactive protein POCT in patients presenting with symptoms of acute respiratory infections in primary care settings. • A systematic review on the analytic performance of commercially available CE-marked C-reactive protein POCT. Systematic searches: The searches will be conducted in line with the EUnetHTA Guideline on Information Retrieval: http://www.eunethta.eu/sites/default/files/Guideline_Information_Retrieval_V1-1.pdf.] To identify relevant studies, systematic searches will be carried out in the following databases: • MEDLINE, Embase, Cochrane Library, (CINAHL via EBSCOHost) • Search of ongoing clinical trials and research projects: Clinicaltrials.gov, International Clinical Trials Registry Platform (ICTRP), UK Clinical Trials gateway. • Ad hoc internet searches to identify relevant grey literature including relevant HTAs • Reference list of included studies, relevant systematic reviews and HTAs will be undertaken For systematic review 1: Search terms related to RTIs will be combined with terms for C-reactive protein and POCT and terms for antibiotic prescribing according to the principles of Boolean logic. Studies will be excluded if they are not conducted in a primary care setting or if C-reactive protein testing is not performed at the point of care. For systematic review 2: Search terms related to C-reactive protein will be combined with terms related to POCT, these will be combined with search terms for diagnostic test accuracy OR analytic performance according to the principles of Boolean logic. For systematic review 3: Search terms related to C-reactive protein will be combined with terms related to POCT, these will be combined with search terms for diagnostic test accuracy OR analytic performance according to the principles of Boolean logic. The Medical Devices Evidence Submission template will be sent to all relevant manufacturers of the technology under assessment. Manufacturers will be asked to submit non-confidential evidence, focusing on the technical characteristics and current use of the technology as well as any non-published studies of the analytical performance of the product. The evidence provided will be used in addition to the literature identified by the literature search. The literature search will be relaunched after completion of the second draft to check for recently

published studies that may be eligible for inclusion. Should such studies be identified, the data will be analysed and their results reported and discussed against the main results of the REA.

Table 2-4: Plan for data extraction

Planned data extraction
Evidence tables for data extraction will be created according to the Cochrane Handbook for Systematic Review of Interventions (Chapter 7.5 - data collection forms)., http://www.cochrane.org/training/cochrane-handbook and http://handbook.cochrane.org/ Data that will be extracted include those listed below. For systematic review 1: Effectiveness and safety • Study characteristics (study author and title, year of publication, study design and length of follow-up, country and setting, inclusion and exclusion criteria, funding source) • Participant characteristics (number of participants, non-respondents/loss to follow up, age, gender, presenting symptoms) • Intervention characteristics (type of C-reactive protein POCT device, algorithm, or CRP cut-point used in study to determine when antibiotics should be prescribed), • Comparator (description of 'standard care') • Outcomes of interest (e.g. number of patients given antibiotic prescriptions (delayed +immediate) for acute RTI (at index consultation and at 28-days follow up), patient mortality at 28 days follow up) Measures of treatment effect: The effect will be reported as a risk ratio with 95% confidence intervals for each dichotomised outcome. When results cannot be pooled, the results will be presented qualitatively. Where it is appropriate to pool data, Review Manager software will be used to perform meta-analysis. Heterogeneity will be investigated using the I^2 statistic. The choice between fixed and random effects meta-analysis will be based on an assessment of the statistical and clinical heterogeneity across studies. Where substantial statistical heterogeneity is observed and sufficient studies are available, a meta-regression will be considered to explore study characteristics that may be potential sources of heterogeneity. Subgroup analysis: 1. By study type, RCT versus cluster RCT versus observational studies. 2. By age group, children versus adults, younger adults (<65 years) versus older adults (≥65 years). 3. By presenting symptoms, upper versus lower respiratory tract infections 4. By setting, out of hours and those in long term care. For systematic review 2: Diagnostic accuracy • Study characteristics (study author and title, year of publication, study design, country and setting, inclusion and exclusion criteria, funding source) • Population characteristics (e.g. number of participants in the trial, age, gender, presenting symptoms) • Intervention characteristics (type of CRP POCT device, time taken for assay, CRP cut-point used), • Comparator characteristics (e.g., description of diagnostic standard) • Outcomes of interest (e.g. Sensitivity, specificity, NPV, PPV, likelihood ratios, AUC, DOR). Measures of treatment effect: pooled measures of diagnostic accuracy e.g. sensitivity and specificity per RTI type. Where results cannot be pooled the results will be presented qualitatively. Review Manager software will be used to perform the DTA. Heterogeneity will be investigated using the I^2 statistic. If sufficient data are available, the following subgroup analyses will be undertaken: 1. By age

group, children versus adults and younger adults (<65 years) versus older adults (≥65 years). 2. By device type 3. By CRP cut point

For systematic review 3: Analytical performance and ease of use

- Study characteristics (study author and title, year of publication, study design, country and setting, inclusion and exclusion criteria, funding source)
- Population characteristics (e.g. number of participants, age, gender)
- Intervention characteristics (type of CRP POCT device, time taken for assay, ease of use),
- Comparator characteristics (e.g., laboratory standard, other CRP POCT)
- Outcomes of interest (e.g. accuracy and precision, ease of use, suitability for primary care).

Measures of treatment effect: pooled measures of accuracy against a standard laboratory CRP measurement and pooled measures of precision. Where results cannot be pooled the results will be presented qualitatively. Data extracted on ease of use and suitability for primary care will be presented qualitatively.

Review Manager software will be used.

Heterogeneity will be investigated using the I^2 statistic.

Subgroup analysis: 1. By device type

2.2.2 Project Scope

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, will be consulted throughout the assessment process.

Table 2-5a: Project Scope: PICO for systematic review 1 – Effectiveness of using C-reactive protein POCT to guide antibiotic prescribing in patients with acute respiratory infections in primary care settings.

Description	Project Scope
Population	The population of interest is represented by patients of all ages who present with symptoms of acute respiratory tract infection in primary care. Subgroups of particular interest include: children, older adults (≥65 years of age), patients attending out-of-hours (OOH) services and those in Long Term Care (LTC) facilities. ICD-10: J00 – J22 (upper and lower RTI), J40 (bronchitis not specified as chronic or acute), H65-H66 (Otitis media), MeSH: C01.539.739, C08.730 (respiratory tract infection), C09.218.705.663 (otitis media), C07.550.781, C08.730.561, C09.775.649 (pharyngitis), C08.618.248, C23.888.852.293 (cough)

Intervention	C-Reactive Protein (CRP) point-of-care test for use in primary care setting (+/- communication training, +/- education component, +/- other biomarkers) in addition to standard care.
	Testing for CRP may assist the clinician in differentiating between bacterial and viral aetiology and therefore guide antibiotic prescribing. Point of care tests allow the test to be done at the time of consultation with results available within minutes.
	
	Twelve CE-marked quantitative devices and three CE-marked semi quantitative methods will be considered in this assessment:
	
	Quantitative:
	• Orion Diagnostica Oy
	  ○ QuikRead® CRP for use on QuikRead 101 instrument
	  ○ QuikRead go® CRP for use on QuikRead go instrument
	  ○ QuikRead go® CRP+Hb for use on QuikRead go instrument
	• Abbott (Alere)
	  ○ Alere Afinion CRP for use on Afinion AS100 analyser
	  ○ NycoCard CRP test for use with NycoCard READER II
	• EuroLyser
	  ○ CRP assay for use with Cube S analyser
	• Boditech Med
	  ○ CRP assay for iChroma instrument
	  ○ AFIAS CRP for use with AFIAS 1
	• Radiometer Medical ApS
	  ○ CRP assay run on AQT90 Flex
	• Horiba
	  ○ CRP assay run on Microsemi instrument
	• Biosurfit
	  ○ Spinit CRP
	• DiaSys Diagnostic Systems GmbH
	  ○ InnovaStar instrument
	
	Semi-Quantitative methods:
	• Medix Biochemica
	  ○ Actim CRP
	• Servoprax
	  ○ Cleartest CRP strips
	• RPS Diagnostics
	  ○ FebriDx
	
	MeSH-terms: D12.776.034.145, D12.776.124.050.120, D12.776.124.486.157 (C reactive

	protein) , N04.590.874.500 (point of care tests)
Comparison	Standard care alone
Outcomes	***Primary outcomes:*** Prescribing outcomes 1. Number of patients given antibiotic prescriptions (delayed +immediate) for acute RTI (at index consultation and at 28-days follow up) Patient outcomes 1. Number of patients with substantial improvement or complete recovery at seven and 28-days follow-up 2. Patient mortality at 28-days follow up ***Secondary outcomes:*** Prescribing outcomes: 1. Number of patients given an antibiotic prescription for immediate use versus delayed use 2. Number of patients who redeemed a prescription for an antibiotic Patient outcomes: 3. Time to resolution of acute respiratory infection symptoms 4. Adverse drug reactions (ADR), including number of patients reconsulting or hospitalised due to ADR 5. Number of patients with RTI complications resulting in reconsultation 6. Number of patients with RTI complications in need of hospitalisation 7. HRQOL 8. Patient satisfaction 9. Physician satisfaction Rationale; the included outcomes have been identified from systematic reviews.[16, 33] MESH terms: D27.505.954.122.085 (antibacterial agents)
Study design	RCTs, cluster RCTs, non randomised studies, observational studies

Table 2-5b: Project Scope: PICO for systematic review 2 – Diagnostic test accuracy of C-reactive protein POCT for acute RTIs.

Description	Project Scope
Population	The population of interest is represented by patients of all ages who present with symptoms of acute respiratory tract infection in primary care. Subgroups of particular interest include: patients attending out-of-hours (OOH) services and those in Long Term Care (LTC) facilities. ICD-10: J00 – J22 (upper and lower RTI), J40 (bronchitis not specified as chronic or acute), H65-H66 (Otitis media), MeSH: C01.539.739, C08.730 (respiratory tract infection), C09.218.705.663 (otitis media), C07.550.781, C08.730.561, C09.775.649 (pharyngitis), C08.618.248, C23.888.852.293 (cough)
Intervention	C-reactive protein POCT for use in primary care setting (+/- other biomarkers). Testing for CRP may assist the clinician in differentiating between bacterial and viral aetiology and therefore guide the prescription of antibiotics. Point of care tests allow the test to be done at

	the time of consultation with results available within minutes. Any CE-marked C-reactive protein POC quantitative or semi quantitative method will be considered in this assessment: MeSH-terms: D12.776.034.145, D12.776.124.050.120, D12.776.124.486.157 (C reactive protein) , N04.590.874.500 (point of care tests)
Comparison	For the diagnostic test accuracy review, the diagnostic standard used for comparison will be dependent on the acute RTI of interest (microbiological/laboratory/radiological confirmation). Each disease group will be analysed separately.
Outcomes	***Primary outcomes:*** 1. Sensitivity and specificity, 2. Positive and negative predictive values (PPV and NPV) 3. Likelihood ratio 4. Area under the ROC curve (AUC) 5. Diagnostic odds ratio (DOR)
Study design	DTA studies

Table 2-5c: Project Scope: PICO for systematic review 3 – Analytic performance of commercially available CE-marked C-reactive protein POCT. (Please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	The population of interest is represented by patients of all ages who present to primary care.

Intervention	C-reactive protein (CRP) point-of-care test for use in primary care setting (+/- other biomarkers).
	
	Twelve CE-marked quantitative devices and three CE-marked semi quantitative methods will be considered in this assessment:
	Quantitative:
	• Orion Diagnostica Oy
	  ○ QuikRead® CRP for use on QuikRead 101 instrument
	  ○ QuikRead go® CRP for use on QuikRead go instrument
	  ○ QuikRead go® CRP+Hb for use on QuikRead go instrument
	• Abbott (Alere)
	  ○ Alere Afinion CRP for use on Afinion AS100 analyser
	  ○ NycoCard CRP test for use with NycoCard READER II
	• EuroLyser
	  ○ CRP assay for use with Cube S analyser
	• Boditech Med
	  ○ CRP assay for iChroma instrument
	  ○ AFIAS CRP for use with AFIAS 1
	• Radiometer Medical ApS
	  ○ CRP assay run on AQT90 Flex
	• Horiba
	  ○ CRP assay run on Microsemi instrument
	• Biosurfit
	  ○ Spinit CRP
	• DiaSys Diagnostic Systems GmbH
	  ○ InnovaStar instrument

	Semi-Quantitative methods:
	• Medix Biochemica
	  ○ Actim CRP
	• Servoprax
	  ○ Cleartest CRP strips
	• RPS Diagnostics
	  ○ FebriDx
	
	MeSH-terms: D12.776.034.145, D12.776.124.050.120, D12.776.124.486.157 (C reactive protein) , N04.590.874.500 (point of care tests)

Comparison	Standard laboratory C-reactive protein measurement or another C-reactive protein POCT instrument.
Outcomes	***Primary outcome*** Measures of accuracy (level of agreement between the result of one measurement and the true value) and precision (degree of reproducibility of the result) will be extracted for each C-reactive protein POCT device ***Secondary outcomes*** Where available, information on ease of use and suitability for primary care POCT will also be collected and summarised for each device
Study design	Any study reporting on analytical performance

3 Communication and collaboration

The EUnetHTA Intranet (https://eunethta.sharepoint.com/Pages/Home.aspx) will be used as primary communication tool.]

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To internally discuss and reach consensus on the scoping.	29/03/2018	E-meeting	Author(s), co-author(s), dedicated reviewers, observers, project manager (external experts, patients)
First draft of the rapid assessment	*To discuss comments of dedicated reviewers*	*[TBC]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers*
Second draft of the rapid assessment	*To discuss comments from ≥ 2 external clinical experts and manufacturers*	*[TBC]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers; external experts, manufacturers*

3.1 Dissemination plan

The final rapid assessment will be published on the EUnetHTA website:
https://www.eunethta.eu/rapid-reas/

All stakeholders and contributors are informed about the publication of the final assessment by the project manager.
Findings will be proposed for publication / presentation at conferences in peer-reviewed journals and will be included as part of full health technology assessments published at a national level.

3.2 Collaboration with stakeholders

Collaboration with manufacturer(s)

Manufacturers were provided the opportunity to review the preliminary PICO. Following receipt of a signed Confidentiality Undertaking, they were also provided the opportunity to undertake a fact check of the draft project plan. Those manufacturers that have signed a Confidentiality Undertaking will also be provided the opportunity to undertake a fact check of the draft assessment

Collaboration with other stakeholders

Patient representation has been sought to reflect the population of interest in this assessment (patients presenting to primary care with symptoms of acute RTI). Patient Focus, a national patient advocacy charity in Ireland (support@patientfocus.ie) has been identified as an appropriate representative. The organisation provided feedback that was incorporated as part of the project plan. This feedback will also be reflected when discussing the assessment findings.

3.3 Collaboration with EUnetHTA WPs

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project, in order to prepare activities to improve national uptake of the final assessment. Feedback on the WP4 REA process will be asked from the involved parties by WP6 [Quality Management], and this information will be processed by WP6 to improve the quality of the process and output.

3.4 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

Authors, co-authors and dedicated reviewers who declare a specific conflict of interest will be excluded from the whole work under this specific topic. However they still may be included in other assessments.

For external experts, patients or other stakeholders involved, conflict of interest declarations are collected. External experts or patients who declare a specific conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other assessments.

Manufacturer(s) will sign a Confidentiality Undertaking (CU) form regarding the specific project.

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5 Appendix A

5.1 Selected Assessment Elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 5-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment [Yes – critical, Yes or No]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	M	What is C-reactive protein POCT testing?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes	M	For which indications have each of the C-reactive protein POCT instruments/methods received CE-marking?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	Yes	M	What is the claimed benefit of C-reactive protein POCT technology in relation to standard care for guiding antibiotic treatment in patients presenting to primary care settings with symptoms suggestive of an acute RTI? What might be the potential harms or risks of this technology in relation to standard care?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Yes	NM	What is the phase of implementation of C-reactive protein POCT in the various European countries participating in EUnetHTA?
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	Yes	M	Who administers C-reactive protein POCT? In what context is it provided? In what primary care settings is it used (e.g. GP practices, out-of-hours clinics, long term care facilities)
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	No	NM	[REA limited to POCT in primary care settings]
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes	NM	What equipment, supplies and training are needed to implement C-reactive protein POCT in primary care?
A0021	Regulatory Status	What is the reimbursement status of the technology? [This assessment element can be placed either in the TEC OR in the CUR domain]	Yes	NM	What is the reimbursement status of C-reactive protein POCT in primary care in the European countries participating in EUnetHTA?
Health problem and current use of technology					

ID	Topic	Topic Issue	Relevance in this assessment [Yes – critical, Yes or No]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	M	What conditions do acute RTIs comprise and how are these defined? What is antimicrobial resistance and how is it related to antibiotic prescribing patterns?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	Yes	NM	What are the known risk factors for acute RTIs? What factors increase the prevalence of antimicrobial resistance in the population?
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes	M	What is the natural course of acute RTIs? (As RTIs are a collection of specific diagnoses, each diagnosis will be discussed briefly e.g. pneumonia, pharyngitis)
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	M	What are the symptoms and burden of disease of an acute RTI for the patient? (again as RTIs are a collection of specific diagnoses each diagnosis will be discussed briefly e.g. pneumonia, pharyngitis)
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	Yes	NM	What are the consequences of acute RTIs for society? What are the consequences of antimicrobial resistance for society?
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes	M	How are acute RTIs currently diagnosed according to published guidelines from European countries?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	M	How are acute RTIs currently managed according to guidelines from European countries? How are they managed in practice?
A0007	Target Population	What is the target population in this assessment?	Yes	M	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	Yes	M	What is the epidemiology of RTIs across the European Union in primary care settings?
A0011	Utilisation	How much are the technologies utilised?	yes	M (NM for diagnostics)	How much is C-reactive protein POCT currently used in Europe to guide antibiotic prescribing?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes	M	Overlaps with COO8 – patient safety
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes	M	Overlaps with COO8 – patient safety
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	M	Overlaps with COO8 – patient safety
D0011	Function	What is the effect of the technology on patients' body functions?	Yes?	M	Does the use of C-reactive protein POCT to guide antibiotic prescribing lead to reduced adverse events as a

ID	Topic	Topic Issue	Relevance in this assessment [**Yes – critical**, **Yes** or **No**]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
					result of lower antibiotic prescribing rates compared with standard care? Are there differences between the commercially available C-reactive protein POCT instruments/methods in terms of analytical performance or diagnostic test accuracy?
D0016	Function	How does the use of technology affect activities of daily living?	No	NM	
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	M	What is the effect of C-reactive protein POCT on health-related quality of life?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	M	What is the effect of C-reactive protein POCT on disease-specific quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	yes	NM	Were patients satisfied with the use of C-reactive protein POCT to guide antibiotic prescribing for their RTI?
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	yes	M	How safe is the use of C-reactive protein POCT in guiding antibiotic prescribing in comparison with standard care? Does the use of C-reactive protein POCT to guide antibiotic prescribing impact mortality in those presenting with symptoms of an acute RTI compared with standard care? How does C-reactive protein POCT to guide antibiotic prescribing affect the duration and severity of symptoms associated with an acute RTI compared with standard care? Does the use of C-reactive protein POCT to guide antibiotic prescribing impact reconsultation or hospitalisation rates in those presenting with symptoms of an acute RTI compared with standard care? As the skin will be broken to remove a small amount blood, is there a risk of harm to patients from blood borne contamination?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	No	NM	Not relevant to C-reactive protein POCT
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	No	M	Not relevant to C-reactive protein POCT
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	M	What are the susceptible patient groups that are more likely to be harmed through the use of C-reactive protein POCT to guide antibiotic prescribing for acute RTIs?
C0007	Patient safety	Are the technology and comparator(s) associated	No	NM	As the skin will be broken to remove a small amount blood, is there a risk of

ID	Topic	Topic Issue	Relevance in this assessment [Yes – critical, Yes or No]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		with user-dependent harms?			harm to staff from blood borne contamination?
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	No	M for medical devices NM for screening and diagnostics	

5.2 Checklist for potential ethical, organisational, patient and social and legal aspects

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
As the skin will be broken to remove a small amount blood, there is a small risk of harm to patient or staff from blood borne contamination.	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	Yes
As the skin will be broken to remove a small amount blood, there is a small risk of harm to patient or staff from blood borne contamination.	
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
Yes, it requires the use of a test and therefore the time taken to collect the blood sample and run the test would need to be incorporated into the care pathway. It is currently unclear who would administer the test (GP/practice nurse) and it may differ between practices based on the availability of the practice nurse. In either case, use of c-reactive protein POCT is likely to prolong the consultation period, even when the time take to run the test is short. The reimbursement for the cost of purchasing and administering the technology would need to be considered.	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes
Introduction of CRP-point of care testing may lead to changes in the patient care pathway depending on by whom the test is administered and who communicates the test results to the patient. Introduction of delayed prescriptions for patients with equivocal results may be considered which could represent a change in practice.	
3. Social	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new	Yes

	social issues?	
	Yes, the introduction of CRP POCT could potentially lead to inequality of care for different patient groups (e.g. public and private patients) depending on how and for whom the test is reimbursed.	
3.2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4.	**Legal**	
4.1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No