EUnetHTA Joint Action 3 2016-2020

What is the diagnostic accuracy of molecular methods that detect the presence of the SARS-CoV-2 virus in people with suspected COVID-19

Project ID: ***RCROT02***

Project description and planning

Health Technology Wales

Healthcare Improvement Scotland

Austrian Social Insurance

This report is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

Version Log

Version number	Date	Modification	Reason for the modification
V1	15/07/2020	Initial draft of the project plan	
V2	27/07/2020	Final draft of the project plan	Feedback implemented based on internal scoping e-meeting with the assessment team
V3	31/07/2020	Final project plan	Feedback from internal review (by co-authors and dedicated reviewers) implemented
V4	08/10/2020	Final project plan including revised timelines	Updated timelines due to high number of included studies that required data extraction and extended statistical analyses

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List of abbreviations

AIHTA	Austrian Institute for Health Technology Assessment
ASI	Austrian Social Insurance (former HVB)
AUC	Area under the curve
CE	Conformité Européenne
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRISPR	Clustered regularly interspaced short palindromic repeats
DOICU	Declaration of Interest and Confidentiality Undertaking
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded deoxyribonucleic acid
E	Envelope (SARS-CoV-2 structural protein)
EUnetHTA	European Network for Health Technology Assessment
HIS	Health Improvement Scotland
HIQA	Health Information and Quality Authority
HTA	Health technology assessment
HTW	Health Technology Wales
ICTRO	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment
IVD	In vitro diagnostic
JA	Joint Action
KCE	Belgian Health Care Knowledge Centre
LAMP	Loop-mediated isothermal amplification
MERS	Middle East respiratory syndrome
mRNA	Messenger ribonucleic acid
N	Nucleocapsid (SARS-CoV-2 structural protein)
NAAT	Nucleic acid amplification test
NPV	Negative predictive values
ORF1ab	Open reading frame 1ab
OT	Other Technologies
PCR	Polymerase chain reaction
PMC	PubMed Central
PPV	Positive predictive values
PROSPERO	International Prospective Register of Systematic Reviews
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCR	Rapid collaborative Review
RdRp	RNA-dependent RNA polymerase
REA	Relative Effectiveness Assessment
RER	Regione Emilia-Romagna
ROB	Risk of bias
ROC	Receiver Operating Characteristics Curve
RNA	Ribonucleic acid
RPA	Recombinase polymerase amplification
RT-PCR	Reverse transcription polymerase chain reaction
S	Spike (SARS-CoV-2 structural protein)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SR	Systematic review
WHO	World Health Organization

1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Health Technology Wales – HTW	Author	United Kingdom	All process steps of assessment and writing draft of report
2.	Healthcare Improvement Scotland – HIS	Co-Author	United Kingdom	Support production of report, review and comment on all drafts
3.	Austrian Social Insurance – ASI	Co-Author	Austria	Support production of report, review and comment on all drafts
4.	Regione Emilia-Romagna – RER	Dedicated Reviewer	Italy	Review and comment on all drafts
5.	Health Information and Quality Authority – HIQA	Dedicated Reviewer	Ireland	Review and comment on all drafts
6.	Belgian Health Care Knowledge Centre – KCE	Dedicated Reviewer	Belgium	Review and comment on all drafts
7.	Austrian Institute for Health Technology Assessment – AIHTA	Project Manager	Austria	Co-ordination between involved parties throughout the assessment period

1.2 Milestones and Deliverables

Given the urgency and importance for public health, the timelines for this project have been pragmatically reduced to an acceptable minimum. The project will not include any patient or public involvement, clinical expert input or review or consultation with manufacturers.

Table 1-2: Milestones and Deliverables

Milestones/Deliverables	Start date	End date	Time*
Project duration	**09-Jul-2020**	**17-Nov-2020**	**92 days**
Scoping and drafting the first version of the project plan	09-Jul-2020	16-Jul-2020	6 days
Milestone 1: Scoping and Kick-off meeting		**17-Jul-2020**	
Finalising protocol and methods as a result of scoping	20-Jul-2020	22-Jul-2020	3 days
Finalising project plan	23-Jul-2020	27-Jul-2020	3 days
Quality checks & editing of project plan	28-Jul-2020	31-Jul-2020	4 days
Milestone 2: Publication of project plan		**31-Jul-2020**	

Milestones/Deliverables	Start date	End date	Time*
Literature search strategy	3-Aug-2020	4-Aug-2020	2 days
Literature strategy cross-checking	5-Aug-2020	6-Aug-2020	2 days
Literature searches	07-Aug-2020	14-Aug-2020	6 days
Literature screening	17-Aug-2020	28-Aug-2020	10 days
Data extraction: Study results and characteristics	31-Aug-2020	25-Sep-2020	20 days
Data extraction: Risk of bias	28-Sep-2020	05-Oct - 2020	6 days
Milestone 3: Data extraction complete		**05-Oct - 2020**	
Statistical analyses & meta-analyses	06-Oct-2020	19-Oct-2020	10 days
Writing first draft rapid assessment	20-Oct-2020	2-Nov-2020	10 days
Milestone 4: First version complete		**2-Nov-2020**	
Internal review of report	3-Nov-2020	6-Nov-2020	4 days
Finalising report including quality checks & editing	9-Nov-2020	16-Nov-2020	6 days
Milestone 5: Publication of report		**17-Nov-2020**	

2 Project Outline

2.1 Project Background

In December 2019, a novel coronavirus was discovered in Wuhan, Province of Hubei, China and has rapidly spread ever since across the world. This novel coronavirus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causes a disease called coronavirus disease 2019 (COVID-19). Currently, diagnostic tests are divided into two main categories, including:

- Tests that detect the presence of SARS-CoV-2 pathogen. These tests can be used to diagnose people with an active COVID-19 infection that either present with signs or symptoms of the disease or that have been in contact with a diagnosed case of COVID-19.
- Tests that detect the presence of antibodies to SARS-CoV-2 pathogen. Antibodies are produced after initial SARS-CoV-2 infection; the time from infection to antibody production is typically 7 to 14 days. These tests can be used to diagnose suspected COVID-19 cases after infection, and to give an indication of whether immunity has developed.

As previously indicated in RCROT01, the pathogen detection tests are further divided into three categories, including: molecular tests or methods that detect the presence of viral RNA (reverse-transcriptase polymerase chain reaction – RT-PCR, isothermal RNA amplification and genetic sequencing), antigen detection tests and viral cultures (1). Currently, the WHO recommends routine confirmation of suspected cases of COVID-19 based on the detection of the unique sequences of the viral RNA by nucleic acid amplification tests (NAAT) such as RT-PCR with further confirmation by nucleic acid

sequencing when necessary or feasible (2). Although some antigen detection tests have been developed, these tests along with genetic sequencing and viral culture approaches are currently not recommended for routine diagnostic procedures (2). Nevertheless, the laboratory processing of the NAAT is complex and results are generally available within 24 hours, posing a great strain on facilities. Molecular tests using different methods or commercial-available kits are being developed and marketed in order to increase the capacity and speed up processing and delivery of results.

The purpose of this rapid review will be to identify, assess and summarise evidence on the performance and diagnostic accuracy of the molecular tests and methods based on NAAT for the diagnosis of a suspected infection with SARS-CoV-2. The work is part of the project undertaken by the EUnetHTA task force on SARS-CoV-2 addressing the following policy priority questions:

- how to best test patients with clinical manifestations of SARS-CoV-2 in order to confirm a diagnosis of COVID-19
- how to best screen asymptomatic subjects and monitor close contacts in order to promptly detect infections among the general population

The evaluation of diagnostic accuracy and performance of different molecular tests and methods in the context of this review will allow to ascertain the best ways to identify new infection, rule out the possibility of infection or identify people in need of care escalation for the management of the pandemic.

2.2 Molecular methods for SARS-CoV-2 detection

The accurate detection of the SARS-CoV-2 pathogen and diagnosis of COVID-19 remains critical for the prevention, early intervention, treatment and control of the pandemic. In medical diagnosis, nucleic acid detection-based approaches are the most rapid and reliable technology for the diagnosis of viral infections. PCR is considered the gold standard method for the detection of viruses as it is characterised by a high sensitivity and specificity (3). RT-PCR is of great interest for the detection of SARS-CoV-2 due to its benefits and adequate sensitivity for the detection of the pathogen in a simple qualitative assay. Real-time RT-PCR is currently favoured for the detection of the pathogen as it provides a simple, specific and quantitative assay for the detection of SARS-CoV-2 (4). Currently, WHO recommends routine confirmation of cases of COVID-19 based on detection of unique sequences of the virus RNA by NAAT (5).

Coronaviruses are positive-stranded RNA viruses that express replication and transcription complexes, including RNA-dependent RNA polymerase (RdRp) from a single, large open reading frame (ORF1ab) and structural proteins such as the envelope (E), nucleocapsid (N) and spike (S) proteins that are expressed via the production of sub-genomic mRNAs which outnumbers the anti-genomic RNA during certain stages of the replication cycle. The ORF1ab/RdRp, E, N and S genes are the targets most frequently used for the detection of SARS-CoV-2 by RT-PCR (6). According to WHO, laboratory confirmation of positive cases of COVID-19 by NAAT should satisfy one of the following conditions:

- “A positive NAAT result for at least two different targets on the COVID-19 virus genome of which one target is preferably specific for COVID-19 virus using a validated assay” OR
- “One positive NAAT result for the presence of betacoronavirus, and COVID-19 virus further identified by sequencing partial or whole genome of the virus as long as the sequence target is larger or different from the amplicon probed in the NAAT assay used” (5).

The sample types recommended by WHO for the detection of the SARS-CoV-2 pathogen by NAAT include lower respiratory tract samples (sputum, aspirate, lavage) and upper respiratory tract samples (nasopharyngeal/oropharyngeal swabs and nasopharyngeal wash or aspirate). WHO indicates that consideration should be given to stools, whole blood, urine and materials from autopsies (5).

WHO acknowledges that the dramatic increase in the number of suspected cases intensified COVID-19 molecular testing, leading to a global shortage of molecular testing reagents for COVID-19 and other molecular diagnostics. Beyond the supply issues, significant limitations of absorption capacity have been recognised in many regions, especially in low- and middle-income countries (2). Furthermore, it has been demonstrated that SARS-CoV-2 evolves in vivo post-infection which in turn affects its virulence, infectivity

and transmissibility (7). Although efforts have been made in order to design primers for RT-PCR assays based on conserved regions of the viral genome, the variability causing mismatches between the primers, probes and target sequences can lead to a decrease in the assay diagnostic performance and the introduction of potential false-negative results (3). Several types of RT-PCR kits have been developed and were rapidly granted approval for use; however, it is widely acknowledged that the quality of these kits is variable and the sensitivity and specificity of the RT-PCR test is not 100%. As a molecular method, RT-PCR has also many limitations including the requirement for highly skilled staff and laboratory instrumentation for processing as well as long reaction times. In a recent report HIQA acknowledges that those disadvantages limit the practical application of RT-PCR approaches and can delay the rapid identification and isolation of individuals with COVID-19 and can thereby contribute to disease transmission (1). These practical limitations of RT-PCR as a molecular method can also explain some of the false-negative results.

A promising alternative to RT-PCR is isothermal amplification which does not require thermocycling. Two isothermal techniques are widely used for rapid and sensitive diagnostic, including loop-mediated isothermal amplification (LAMP) and recombinase polymerase amplification (RPA) (8). LAMP uses a strand-displacing DNA polymerase with four specially designed primers that contain regions of complementarity to six target sequences while RPA uses a recombinase that catalyses strand invasion of a primer into dsDNA. The recently published HIQA report acknowledges that no CE-marked RT-LAMP technologies were identified at the time of publication; however, a number were reported to be in development (1).

Lastly, the RNA-targeting clustered regularly interspaced short palindromic repeats (CRISPR) associated enzyme Cas13 has been adapted for rapid and portable detection of nucleic acid. Two novel detection techniques called SHERLOCK and DETECTR have been reported to have comparable accuracy to real-time RT-PCR (1, 4). Nevertheless, molecular methods using CRISPR Cas12 systems are still in development and are not yet used in clinical settings.

2.3 Project Objectives

The purpose of this rapid review will be to identify, assess and summarise evidence on the performance and diagnostic accuracy of the molecular tests and methods based on NAAT for the diagnosis of a suspected infection with SARS-CoV-2. The work is part of the project undertaken by the EUnetHTA task force on SARS-CoV-2 addressing the following policy priority questions: (1) how to best test patients with clinical manifestations of SARS-CoV-2 in order to confirm a diagnosis of COVID-19 and (2) how to best screen asymptomatic subjects and monitor close contacts in order to promptly detect infections among the general population. It is now widely admitted that huge efforts need to be made in order to scale up the current COVID-19 testing protocols. Hence, there is a clear need to evaluate alternative molecular methods and approaches to allow NAAT to continue in the face of these potential challenges and shortages. The evaluation of diagnostic accuracy and performance of different molecular tests and methods in the context of this review will allow to ascertain the best ways to identify new infection, rule out the possibility of infection or identify people in need of care escalation for the management of the pandemic.

2.4 Project Method and Scope

2.4.1 Approach and Method

Table 2-1: Project approach and method

Project approach and method
The following studies will be searched and considered for inclusion: • Retrospective and prospective cohort, case series/case control studies (with a minimum of 10 participants) and cross-sectional studies evaluating diagnostic accuracy and performance of molecular tests for the detection of SARS-CoV-2 • Studies testing possible or suspected incident cases of COVID-19 for diagnosis on the basis of clinical symptoms, contact tracing or as part of mass screening • Index test and reference standard must be tested simultaneously using the same clinical specimen type from a patient • Only studies providing sufficient data to construct a 2x2 diagnostic table (true positives, true negatives, false positives and false negatives) • Published peer-reviewed journal articles and non-peer-reviewed manuscript preprints will be included as well as assessment reports by national/international regulatory agencies • Evidence published in any language will be screened; however, if an adequate English translation is not available then the studies will be excluded • Only evidence published from January 2020 onwards **Other considerations for study selection include:** • Evidence on the accuracy of diagnosing COVID-19 based on clinical information alone, eg signs and symptoms, chest imaging will be excluded • Tools used for mass non-contact screening such as fever screening at airports or other transit hubs will be excluded • Studies on previous SARS coronavirus types and on Middle East Respiratory Syndrome (MERS) will be excluded • Studies evaluating the same test on different clinical specimens or sites will be excluded • Studies testing previously diagnosed COVID-19 patients for the purpose of monitoring will be excluded • Studies that follow a serial sampling design will be excluded unless they provide extractable data points for initial diagnosis **Risk of bias:** • The quality of the studies will be assessed using the QUADAS-2 tool for the following four domains: patient selection, index test, reference standard and flow and timing. **Data analysis:** • If appropriate and the data is suitable, primary analysis of diagnostic accuracy will be based on bivariate meta-analysis of sensitivity and specificity. If sufficient data for a bivariate meta-analysis is not available, univariate meta-analysis will be applied. • If suitable, we will conduct subgroup analysis to assess variables that potentially affect test accuracy, such as but not limited to overall study quality, sample selection or type, quantitative or qualitative reporting of results, any variation in test performance in different populations, including but not limited to: o Symptomatic versus asymptomatic/pauci-symptomatic identified from contact tracing/mass screening of the general population o A range of different genetic, ethnic or demographic factors

- Clinical specimen or sample site
- Self-administered tests versus those administered and/or interpreted by a healthcare professional.

Table 2-2: Plan for the retrieval of evidence

Literature search strategy
A systematic information retrieval for relevant studies or documents is carried out to obtain comprehensive information. The following sources of information as well as search techniques are considered: **Main information sources** Bibliographic databases: • Medline • Embase • CENTRAL (Cochrane) Study registries: • Cochrane COVID-19 Study Registry – encompassing: o U.S. National Institutes of Health: ClinicalTrials.gov o World Health Organization: International Clinical Trials Registry Platform – COVID-19 trials • EU Clinical Trials Registry Some COVID-19 specific registries have been included, especially as the standard ICTRP site is not currently available. **Further information sources and search techniques** To identify further relevant studies or documents, depending on the research question, further information sources are used and further search techniques are applied: • Checking reference lists of relevant systematic reviews (SRs) / HTAs • Searching preprint servers (Europe PMC) • Searching relevant websites (e.g. HTA bodies, INAHTA HTA database) • Queries to authors **Selection of relevant studies and documents** EndNote X8.2 is used for citation management. Study selection will be performed in Covidence. All selection steps are performed by 2 persons independently of each other. Discrepancies are resolved by discussion.

Table 2-3: Plan for data extraction

Planned data extraction
Based on the guidance provided by Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (2020) (20), the following data will be extracted • Author and year of publication • Study design, type of recruitment (prospective or retrospective) • Study population characteristics, including sample size, country and the clinical context in which the test was evaluated • Definition of the reference standard • Clinical specimen or sample site • Timing of sample relative to onset of symptoms or since contact for contact tracing

episodes (if relevant)
- Technical specifications, gene target(s) and diagnostic threshold used in the study
- Detection used and technical performance data, when available
- Information regarding quality assessment items of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool
- Data to enable derivation of 2×2 tables of the number of true positives, false positives, false negatives, and true negatives

2.4.2 Project Scope

The EUnetHTA Guidelines, notably the Methodology Guideline "Meta-analysis of diagnostic accuracy studies", available at https://www.eunethta.eu/methodology-guidelines/ will be consulted throughout the assessment process.

Table 2-4: Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	Possible or suspected incident cases (any age but where possible categorised as paediatric if age<18 and adult if age≥18) of COVID-19 tested for diagnosis on the basis of clinical symptoms, contact tracing or as part of mass screening.
Target condition	Active infection with SARS-CoV-2
Index tests	Any molecular assay based on nucleic acid amplification tests, such as RT-PCR or isothermal RNA amplification methods, that is designed to detect the presence of SARS-CoV-2 infection in people with suspected COVID-19.
Reference standard	• RT-PCR conducted on specific targets of SARS-CoV-2 virus using a validated assay, alone or in combination with clinical findings
Outcomes	• Sensitivity (95% CI) • Specificity (95% CI) • Area under the curve from receiver-operator characteristic curve (ROC curve) • Proportion of true/false positive participants and true/false negative participants • Positive predictive values (PPVs) and negative predictive values (NPVs) (95% CI) • Proportion of inconclusive test results
Study design	Retrospective and prospective cohort, case series/case control studies (with a minimum of 10 participants) and cross-sectional studies evaluating diagnostic accuracy and performance of molecular tests for the detection of SARS-CoV-2

The following aspects were taken into consideration for the PICO design:

- Study design:
  - The minimum number of participants established for the studies that follow a case series/case control design was based on a subsequent pooled analysis conducted by HTW (submitted and awaiting publication), where it was found that excluding small

studies (n<=10) produced results concordant with earlier published meta-analyses whilst excluding only a small number of patients (46 patients across 7 studies). Given the likely increase in available data excluding n<= 10 is a reasonable and pragmatic approach that will exclude small studies that are also likely to have issues with bias and reliability.

- Reference standard:
  - If feasible, any insights provided from authors on discordant findings between index test and reference standard will be narratively and briefly recorded, as they may provide useful information for comments on future research.

Table 2-5: Data Extraction – Study Characteristics

Study ID, Author, year	
Characteristics of study	
Design	Study design Inclusion criteria Exclusion criteria
Stated objective	Quote from publication
Participants characteristics and setting	Number of participants Proportion of participants with no symptoms or signs for COVID-19 Proportion of participants with symptoms and signs for COVID-19 Proportion of participants identified through contact tracing Mean (SD)/median (quartile range) time from occurrence of symptoms to time of diagnosis/test Proportion of males and females Age (mean, SD) List of countries Symptoms related to COVID-19 Date of the sample Setting
Target condition	
Reference standard	
Index test	(Commercial) name of index test

	Name of manufacturer Regulatory status (e.g. CE-IVD) Test format Target Sample type (e.g. nasopharyngeal) Reported cut-off values Reported analytical sensitivity/limit of detection Reported analytical specificity/cross-reactivity
Flow and timing	
Publication details	Language of publication Funding Publication status
Notes	

Table 2-6: Data Extraction – Results

Study ID, Author, year	
Results	
Diagnostic accuracy	Sensitivity (95% CI) Specificity (95% CI) Area under the curve (AUC) from a receiver operating characteristics curve (ROC curve) Absolute and relative number of true-positive participants Absolute and relative number of false-positive participants Absolute and relative number of true-negative participants Absolute and relative number of false-negative participants Positive and negative predictive values (95% CI)
Authors' conclusions	

2.4.3 Risk of Bias

The risk of bias is assessed for each individual study that satisfies the inclusion criteria. The QUADAS-2 tool for the quality assessment of diagnostic accuracy studies will be used. The results are described, merged and analysed.

2.4.4 Statistical Analysis

Any statistical analysis will follow the recommendations in the EUnetHTA Methodology Guideline "Meta-analysis of diagnostic test accuracy studies", available at https://www.eunethta.eu/methodology-guidelines/. For the purpose of cohesiveness, the statistical analysis approaches will follow the ones adopted in RCR OT 01. If appropriate and feasible we will compute the following:

- 95% confidence intervals will be calculated for the measures of accuracy (sensitivity, specificity, positive and negative predictive values)
- Univariate meta-analysis will be performed for the AUC
- The primary meta-analysis will be a bivariate meta-analysis with random effects. If data is not sufficient for a bivariate meta-analysis, separate univariate meta-analysis will be performed.
- Subgroup analysis for variables that might affect the accuracy or performance of tests will be conducted using meta-regression approaches
- Narrative summaries will be provided if meta-analyses approaches cannot be applied in a meaningful way due to pronounced heterogeneity.

3 Communication and collaboration

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping and Kick-off Meeting	To internally discuss and reach consensus on the scoping. To discuss the preliminary PICO and draft project plan	17/07/2020	E-meeting	Author(s), co-author(s), dedicated reviewers, project manager
Data Extraction Milestone	To discuss the approach to data analysis and results section depending on the identified literature	[DD/MM/YYYY]	E-meeting	Author(s), co-author(s), dedicated reviewers, project manager
Final Draft of the Rapid Assessment	To discuss amendments and changes to the final draft of the rapid assessment	[DD/MM/YYYY]	E-meeting	Author(s), co-author(s), dedicated reviewers, project manager

3.1 Dissemination plan

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

All partners and contributors are informed about the publication of the final assessment by the project manager.

This project will be registered on PROSPERO. Publication in a peer-reviewed journal will be attempted if feasible.

3.2 Conflict of interest management

All authors, co-authors and dedicated reviewers involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form, which was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

4 References

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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 have been screened and included/ merged with the existing questions if deemed relevant. Given the time constraints and the nature of the pragmatic approach for publishing evidence on COVID-19 during the pandemic, only the most basic elements have been included even if more elements are considered mandatory under routine circumstances. The questions listed will be cross-checked for the retrieval and reporting of information. This approach is consistent and in line with the RCR OT 01 for antibody testing.

Table 5-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?		M	
B0001	Features of the technology and comparators	What is the technology and the comparator(s)? Are the reference values or cut-off points established?	Are the conflicting definition of abnormal findings likely to affect the results interpretation?	M	
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?		NM	
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?		M	
A0004	Target Condition	What is the natural course of the disease or health condition?		M	
A0006	Target Condition	What are the consequences of the disease or health condition for the society?		NM	
A0007	Target Population	What is the target population in this assessment?		M	
Test accuracy					
D1001	Test accuracy	What is the accuracy of the test against reference standard?		M	
D1002	Test accuracy	How does the test compare to other optional tests in terms of accuracy measures?		M	
D1003	Test accuracy	What is the reference standard and how likely does it classify the target condition correctly?		M	
D1004	Test accuracy	What are the requirements for accuracy in the context the technology will be		M	

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		used?			
D1005	Test accuracy	What is the optimal threshold value in this context?		M	
D1006	Test accuracy	Does the test reliably rule in or rule out the target condition?		M	
D0014	Function	What is the effect of the technology on work ability?		M	
D0015	Function	What is the effect of the technology on return to previous living conditions?		M	
Safety					
C0006	Patient Safety	What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?		M	
C0020	Occupational safety	What kind of occupational harms can occur when using the technology?		NM	
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?		M	
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)?		NM	