# SCREENING OF FETAL ANEUPLOIDIES WHEREBY NON-INVASIVE PRENATAL TEST (NIPT)

***Project ID: OTCA03***

## Project description and planning

**Authors: Scientific Advice Unit, avalia-t, Galician Agency for Health Technology Assessment-ACIS, Spain**

**Co-authors: Regione Emilia-Romagna-RER, Italy**

# Contents:

# A. VERSION LOG

| Version number | Date | Name (Initials) | Modification | Reason for the modification |
|---|---|---|---|---|
| V1 | 01/12/16 | LVL | First version of draft project plan | - |
| V2 | 09/12/16 | LVL | Revised draft project plan | Comments received from co-authors |
| V3 | 23/12/16 | LVL | Revised draft project plan | SABA e-meeting/discussions with co-authors, dedicated reviewers |
| V4 | 28/02/17 | LVL | Revised draft project plan | Comments from stakeholders (external experts and manufacturers) |
| V5 | 22/03/17 | LVL | Amendments and final project plan | - |
| V6 | 02/06/17 | LVL | Amendments of timelines | Update of timelines. |

# B. PROJECT PLAN

## 1.0 PARTICIPANTS

All individuals actively participating in the project.

Table 1. Project participants

| # | Agency | Country | Role in the project | Individual's expertise | Distribution of work |
|---|---|---|---|---|---|
| 1. | Scientific Advice Unit, avalia-t | Spain | Author(s) | Evidence-based medicine, systematic reviews, HTA reports and clinical practice guidelines development | See project approach |
| 2. | Regione Emilia-Romagna, RER | Italy | Co-Author(s) | Evidence-based medicine, systematic reviews, HTA reports and clinical practice guidelines development | See project approach |
| 3. | DEFACTUM-MIDT Social & Health Services and Labour Market | Denmark | Dedicated Reviewer | Evidence-based medicine, systematic reviews, HTA | See project approach |
| 4. | Swiss Network of HTA (SNHTA) | Switzerland | Dedicated Reviewers | Expertise in evidence-based medicine, systematic reviews, HTA reports and statistical analysis | See project approach |
| 5. | National Institute of Pharmacy and Nutrition (NIPN) | Hungary | Dedicated Reviewer | Evidence-based medicine, systematic reviews, HTA reports and clinical practice guidelines development and development of legal regulations | See project approach |
| 6. | Institute for Quality and Efficiency in Health Care (IQWiG) | Germany | Dedicated reviewer | Expertise in evidence-based medicine, systematic reviews, HTA reports | See project approach |

| | | | | | |
|---|---|---|---|---|---|
| 7. | National Organization for Healthcare Provision (EOPPY) | Greece | Observer | | See project approach |
| 8. | Comité Gallego de Bioética | Spain | External expert | Bioethical Expert | See project approach |
| 9. | Fundación Pública Galega de Medicina Xenómica | Spain | External experts | Specialists in Human Laboratory Genomic DNA testing (2 experts) | See project approach |
| 10. | Commissione Nascita Regione Emilia-Romagna | Italy | External expert | Clinical (physician specialist in gynecology and obstetrics) | See project approach |
| 11. | University Hospital of Zurich | Switzerland | External expert | Clinical (physician specialist in obstetrics) | See project approach |
| 12. | Scientific Advice Unit, (avalia-t) | Spain | Project coordinator | Project management | See project approach |
| 13. | Ludwig Boltzmann Institute for HTA (LBI-HTA) | Austria | Project coordinator | Project management | See project approach |

## 1.1 PROJECT STAKEHOLDERS

Table 2. Project stakeholders[♣]

| Organisation's name | Type of organisation |
|---|---|
| Sequenom Laboratories, San Diego, CA, USA | Manufacturer |
| Ariosa Diagnostic (Roche Diagnostic, Switzerland) | Manufacturer |
| Natera, San Carlos, CA, USA | Manufacturer |
| Premaitha Health, UK | Manufacturer |
| Illumina Inc, San Diego, CA, USA | Manufacturer |
| Imegen, Spain | Manufacturer |
| Vanadis Diagnostic, Sweden | Manufacturer |
| Genesupport, Switzerland | Manufacturer |
| NIPD Genetics, Cyprus | Manufacturer |
| Berry Genomics, China | Manufacturer |

♣ Here the term "stakeholder" has a generic meaning that goes beyond (yet may include) the identified EUnetHTA Stakeholder groups (as described in the EUnetHTA Stakeholder Policy).

  

| Organisation's name | Type of organisation |
|---|---|
| Igenomix, Spain | Manufacturer |
| Genoma, Italy | Manufacturer |
| Ebios Futura S.R.L., Italy | Manufacturer |
| Sorgente Genetica, Italy | Manufacturer |
| Mutiplicom, Belgium | Manufacturer |
| LifeCodexx, Germany | Manufacturer |
| LabCorp, Inc., USA | Manufacturer |
| BGI Diagnostic, China<br>High risk pregnant woman, Spain | Manufacturer<br>User representative |

## 2.0 PROJECT INTRODUCTION/ RATIONALE

| Project introduction/ rationale |
|---|
| The rationale for this assessment report is to produce collaborative assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of non-pharmaceutical health technologies. In addition, the implementation of the jointly produced assessment in the national/regional practice will be facilitated. |

## 3.0 PROJECT SCOPE AND OBJECTIVES

| | List of project objectives | Indicator (and target) |
|---|---|---|
| 1. | To produce collaborative health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies. | Production of 1 rapid collaborative relative effectiveness assessment (REA) according to the research question (see Table 3). |
| 2. | To compile a rapid REA of non-invasive prenatal test (NIPT). | Production of a rapid REA of non-invasive prenatal test (NIPT).<br>NIPT is considered to provide a new non invasive screening option for prenatal screening, because it could provide higher accuracy than standard combined tests, avoiding unnecessary recourse to amniocentesis or chorionic villus sampling, which carry risks of miscarriage or harm to the unborn child. The impact on prenatal screening is expected to be high. |

| | | |
|---|---|---|
| 3. | To refine the production processes of collaborative assessment reports based on lessons learned and experiences from JA2 and probe a stepped roll-out of additional collaborative assessments yielding timely information. | Development of sustainable production processes for collaborative assessments. Production of collaborative assessments probing a decentralized coordination process and facilitating to meet national timelines. |
| 4. | To develop a process that facilitates the implementation of the collaborative assessment in the national/regional practice. | Production of >2 national/local reports based on the collaborative assessment. |

The research question addressed by this REA is whether prenatal screening with non-invasive prenatal test (NIPT) in pregnancy population is more effective and/or safer than prenatal screening based on combined test.

Table 3. Project Scope: PICO

| Description | Project scope |
|---|---|
| **Population** | Pregnant women at least 8-9 weeks' gestation undergoing routine primary screening for fetal aneuploidies<br><br>Three types of population will be considered in this assessment:<br><br>1. Pregnant women classified as high risk for fetal aneuploidies by combined test results (first and/or second trimester serum screening and/or nuchal translucency), or assessed as high risk as a result of advanced maternal age, family history of chromosome abnormality, previous aneuploid pregnancy history.<br><br>Threshold cut-off values for defining high risk women: >1:300<br><br>2. Pregnant women classified as intermediate risk for fetal aneuploidies by combined test results (first and/or second trimester serum screening and/or nuchal translucency),<br><br>Threshold cut-off values for defining intermediate risk: 1:300-1:1000<br><br>3. General pregnant population without any pre-defined fetal |

| | |
|---|---|
| | aneuploidy risk factor.<br><br>Women with ultrasound findings indicative of major fetal malformations will be excluded<br><br>• The following subgroups analyses will be considered:<br><br>o Pregnant women screened during the first trimester<br>o Pregnant women screened after first trimester<br>o Singleton pregnancies<br>o Twin pregnancies<br>o Pregnant women after assisted fertilization<br>o Pre-test trisomy group<br>o Mother´s age<br><br>Rationale: According to guidelines from the National Society of Genetic Counsellors (NSGC) [1] and The American College of Obstetricians and Gynaecologists (ACOG) [2], position statements from the International Society for Prenatal Diagnosis [3] and (ACOG)-Society for Maternal-Fetal Medicine [4], NIPT could be offered to pregnant women at high risk of aneuploidy or general obstetric population. The International Society for Prenatal Diagnosis (ISPD) considers NIPT could be used as a primary test, offered secondary to a high risk assessment or contingently to women ascertained as having high or intermediate risk by conventional screening"[5]. Some organizations, like NICE, also recommend these tests for high or intermediate risk (https://www.nice.org.uk/guidance/cg62/chapter/1-Guidance#screening-for-fetal-anomalies). NIPT would not be applicable in triplet and higher order pregnancies. |
| **Target condition** | ICD-10 codes:<br><br>o Trisomy 21: ICD-10-CM Diagnosis Code Q90 (Q90.0, Q90.1, Q90.2 y Q90.90<br>o Trisomy 18: ICD-10-CM Diagnosis Code Q91 (Q91.0-3)<br>o Trisomy 13: ICD-10-CM Diagnosis Code Q91 (Q91.4-7)<br><br>MesH terms: aneuploidy, trisomy 21, trisomy 18, trisomy 13, Down syndrome, Edward syndrome, Patau syndrome |
| **Interventions:** | Five types of interventions will be assessed: |

| | |
|---|---|
| | 1. Prenatal screening based on NIPT to estimate risk of fetal aneuploidies, followed - for women testing at risk - by invasive diagnostic tests (NIPT as a primary testing method; total replacement of combined tests).<br><br>2. Prenatal screening based on NIPT, nuchal translucency and other clinical information (family history of chromosome abnormality, previous aneuploid pregnancy history, etc.) to estimate risk of fetal aneuploidies, followed - for women testing at risk - by invasive diagnostic tests (NIPT as part of a combined test; partial replacement of combined tests).<br><br>3. Prenatal screening based on standard combined test and clinical information (family history of chromosome abnormality, previous aneuploid pregnancy history, etc.) to estimate risk of fetal aneuploidies, followed - for women estimated to be at high risk- by NIPT, followed - for women having risk confirmed by NIPT- by invasive diagnostic tests. (NIPT as an add-on to combined tests and other factors).<br><br>4. Prenatal screening based on standard combined test to estimate risk of fetal aneuploidies, followed - for women testing at intermediate to high risk of aneuploidies- by NIPT, followed - for women having risk confirmed by NIPT- by invasive diagnostic tests (NIPT in add-on to combined tests and other factors).<br><br>5. Prenatal screening and diagnosis with NIPT without confirmation by invasive diagnostic tests (NIPT in replacement of invasive diagnostic tests).<br><br>Non-invasive prenatal tests (NIPT) are based on the analysis of cell-free fetal DNA (cffDNA) in the maternal plasma and are carried out using one of the following techniques:<br>• Next Generation Sequencing (NGS):<br>  ○ Whole Genome Sequencing<br>  ○ Targeted Genome Sequencing: chromosome specific sequencing (CSS) or single nucleotide polymorphism-based method (SNP) |

| | |
|---|---|
| | • Micro array based techniques<br><br>Influence of different techniques and timing on NIPT (first trimester or afterwards) on results will be analysed through a sensitivy analysis<br><br>NIPT trademarks identified: Genatal 1, Genatal 2, Genatal +, Verify™ Prenatal Test, MaterniT21Plus™, MaterniT™ Genome, VisibiliT™, The Harmony™ Prenatal Test, Panorama® Prenatal Screening Test, The IONA® test, Vanadis SMART™ NIPT, Prendia START, Prendia EXTEND, VERACITY™, BambniTest, NACE®, NACE® amplified, PrenatalSafe®, Prenataltest®, Aurora, Clarigo™, PrenaTest® or PraenaTest®, informaSeq™ test, TrisoNIM® Advance, Trisonim® Premium, NIFTY™ test<br><br>MesH terms: cell-free fetal DNA, massively parallel sequencing, single nucleotide polymorphism-based method, non-invasive prenatal testing<br><br>Intended use of technology: prevention |
| **Comparison** | Routine primary screening for fetal aneuploidies based on the risk estimated by standard combined test and/or other risk factors, followed - for women considered to be at risk - by invasive diagnostic tests.<br><br>Combined test relies on:<br>• a maternal serum test for the identification of two biomarkers, pregnancy-associated plasma protein A (PAPP-A) and β-human chorionic gonadotropin (βHCG)<br>• and/or an ultrasound scan to measure fetal nuchal translucency (NT)<br>• and maternal age<br><br>Rationale: comparators have been identified from guidelines mentioned above, i.e. population description [1-2] and EUnetHTA [6]. |
| **Reference Standard** | Fetal karyotype through invasive testing like amniocentesis or chorionic villus sampling<br>Outcome at birth through clinical examination of the newborn or by |

  

| | |
|---|---|
| | karyotyping in case of miscarriage or fetal loss. |
| **Outcomes** | The intervention under assessment is prenatal screening (with different positioning of NIPT) aimed at informing women about the risk of trisomy 13, 18 and 21. The claimed benefit of the tests is to provide information that is more accurate. Effectiveness of the screening process will be evaluated in terms of accuracy (intermediate outcomes), as invasive tests are already a decision based on NIPT results, but also in terms of results of patient-related outcomes, assessing how these screening strategies could impact on the management of prenatal aneuploidies.<br>• **Safety of NIPT for trisomy 13, 18, 21**<br>○ False negative<br>○ False positive<br>○ Increase in the number of children born with other major unconfirmed chromosomal conditions/anomalies (not targeted by prenatal aneuploidies screening)<br>○ Increase in elective pregnancy termination for other unconfirmed chromosomal abnormalities (not targeted by prenatal aneuploidies screening)<br>○ Test performance: test failure rate, uncertain results rate<br>• **Effectiveness of NIPT for trisomy 13,18,21**<br>○ Sensitivity & Specificity<br>○ PPV (positive predictive value)<br>NPV (negative predictive value)<br>• **Effectiveness of prenatal screening with NIPT against screening without NIPT on patient relevant outcomes for the different screening strategies**<br>○ Reduction in children born with undiagnosed 13, 18, and 21 trisomies<br>○ Reduction in the number of miscarriages or still birth of subject affected by 13, 18, and 21 trisomies<br>○ Reduction in the number of miscarriages related to invasive testing (amniocentesis or chorionic villus sampling)<br>○ Reduction in uptake of invasive testing<br>○ Change in uptake of prenatal screening<br>• **Organizational, ethical and social issues of aneuploidy** |

| | |
|---|---|
| | **screening**<br>○ Completion of the diagnostic pathway by 15th week of gestation<br>○ Completion of the diagnostic pathway by 15th week of gestation<br>○ Genetic counseling pre and post aneuploidy screening<br>○ Process related costs<br>• **Other patient important outcomes**<br>○ Anxiety<br><br>Rationale: outcomes have been identified from documents mentioned above [1-3] and EUnetHTA guidelines about selection of endpoints for REA [5]. |
| **Study design** | • **Safety of prenatal screening with NIPT:** randomized controlled clinical trials, non-randomized controlled clinical trials, DTA studies on index test and comparator (cross-sectional studies) and registries<br>• **Effectiveness of prenatal screening with NIPT:** randomized controlled clinical trials, non-randomized controlled clinical trials and DTA studies on index test and comparator (cross-sectional studies)<br>• **Organizational, ethical, legal issues and patient outcomes**: reviews/consensus documents and qualitative studies |

## 4.0 PROJECT APPROACH AND METHOD

Table 4a. Project approach and method

| **Project approach and method** |
|---|
| • The selection of assessment elements will be based on The HTA Core Model® for Rapid Relative Effectiveness Assessment Version 4.2 [6]. Additional elements will be added from the HTA Core Model® Application for Diagnostic Technologies Version 3.0 and the HTA Core Model® Application for Screening Technologies Version 3.0 [7].<br>• A systematic search of the scientific literature will be performed in the following databases: |

Centre for Reviews and Dissemination (CRD) Databases, Cochrane Library Plus.
Medline (PubMed), Embase (OVID), Web of Science (Web of Knowledge) and Scopus.
Search of ongoing clinical trials and research projects: Clinicaltrials.gov, Cochrane Central EU clinical trials, International ClinicalTrials Registry Platform (ICTRP) and UK Clinical Trials gateway.

- Specific search strategies will be designed to identify qualitative studies related to patients' outcomes.

- The short version of the EUnetHTA submission file will be used as starting point for the TEC and CUR domains. In addition, a general search will be performed, scanning multiple data sources for additional information, double checking information for biased data.

- Qualitative studies identified by the systematic literature search will be used for other domains (ETH, ORG, SOC, LEG). Information completed with general internet-searches and manufacturer submission file.

- A hand search of the literature will be performed to identify relevant studies for all domains.

- Literature selection: Two independent reviewers (from avalia-t) will select the papers in accordance with previously defined PICO question. This process will be checked by co-authors.

- Data extraction: The relevant data will be extracted and recorded in evidence tables by one author from avalia-t and reviewed by another. As above, this step will be checked by co-authors.

- Quality of evidence assessment: The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool will be used for diagnostic accuracy studies (DTA studies) [8], the Cochrane risk of bias tool (RoB 2.0 tool) for randomized controlled trials [9] and the Risk of Bias in non-randomized of Interventions tool (ROBINS-I tool) [10] for prospective non-randomized controlled trials. The level of confidence / certainty in the evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [11]. Qualitative studies will be assessed using the CASP checklist [12] and GRADE-CERQual tool [13]. This process will be reviewed by co-authors as well. No quality assessment tool will be used for the TEC, CUR, ETH, ORG, SOC or LEG domains.

- Synthesis of evidence: Quantitative analysis methods used for SAF and EFF domain . Descriptive analysis of information for other domains.

<u>Description of the distribution of responsibilities between authors and co-authors</u>:

Avalia-t

- Develop the first draft of EUnetHTA project plan
- Perform the literature search & study selection
- Carry out the assessment (extraction, analysis, synthesis and interpretation of findings)
- Send draft to reviewers, compile feedback from reviewers and perform changes according to reviewer's comments

- Prepare final assessment and write a final summary of the assessment

RER:

- Collaboration in the development of the EUnetHTA project plan
- Check and approve all steps (e.g. literature selection, data extraction, assessment of risk of bias). Discussion of conclusions, which should be agree upon.
- Review draft assessment, propose amendments where necessary (perform additional hand search if needed) and provide written feedback.

Responsibilities of reviewers

- Review and comment on project plan, propose amendments where necessary
- Rate the relevancy of outcomes (GRADE method)
- Review and comment on draft, propose amendments where necessary

Table 4b. Preliminary Evidence Table

| **Preliminary evidence table** |
|---|
| **Study characteristics** |
| Author |
| Year of publication |
| Study's registration number in clinical trial database |
| Country/ies of recruitment |
| Setting |
| Data collection period |
| Target Population (high risk/ general; singleton/twin) |
| Target condition |
| Target condition prevalence in the enrolled population<br>(information given by Authors or calculated by reviewers) |
| Comparator (standard/combined screening) |
| Cut off for comparator |
| Intervention / index test(trademark) |
| Index test technique |
| Country where samples were sent/analysed |
| Cut off value for NIPT |
| Standard reference (amniocentesis, chorionic villus sampling, cordoncentesis or others) |
| Study design |
| Number of patients |
| **Patient characteristics** |
| Maternal age |

| |
|---|
| Gestational age |
| Pregnancy (singleton or twin) |
| Maternal weight |
| Pregnancy by assisted reproductive techniques |
| Inclusion criteria |
| Exclusion criteria |
| **Outcomes** |
| *Safety test* |
| False negative |
| False positive |
| Increase of children born with other alterations that could lead to birth defects |
| Test performance: test failure rate, uncertain results rate |
| *Effectiveness test* |
| Sensitivity |
| Specificity |
| True negative |
| True positive |
| *Effectiveness prenatal screening with NIPT* |
| Reduction in uptake of invasive testing (amniocentesis or chorionic villus sampling) |
| Reduction of miscarriages rates due to invasive testing |
| Reduction of undiagnosed fetal aneuploidy conditions |
| Change in uptake of/adherence to prenatal screening |
| *Organizational, ethical and social/patient issues of aneuploidy screening* |
| Completion of the diagnostic pathway by 15$^{th}$ week of gestation |
| Genetic counseling pre and post aneuploidy screening |
| Process related costs |
| Screening related anxiety |

| |
|---|
| Risk of bias (from QUADAS-2) |
| Patient selection |
| Was a consecutive or random sample of patients enrolled? |
| Did the study avoid inappropriate exclusions? |
| Index test |
| Were the index test results interpreted without knowledge of the results of the reference standard? |
| If a threshold was used, was it pre-specified? |
| Reference standard |
| Was the appropriate reference standard used to correctly classify the target condition? |

| |
|---|
| Were the reference standard results interpreted without knowledge of the results of the index test? |
| Flow and timing |
| Did all patients receive a reference standard? |
| Were all patients included in the analysis? |
| Concerns regarding applicability (from QUADAS-2) |
| Patient selection |
| Is there concern that the included patients do not match the review question? |
| Index test |
| Is there concern that the index test, its conduct, or interpretation differ from the review question? |
| Reference standard |
| Is there concern that the target condition as defined by the reference standard does not match the review question? |

| |
|---|
| Study results |
| Enrolled women (N) |
| Mean maternal age (range/SD) - year: |
| Mean gestational age (range/SD) - wk: |
| Ethnicity – no. (%) |
| Distribution of population's risk of aneuploidy |
| Single/twin pregnancy (N, %) |
| Type of prenatal screening (other than NIPT) - no. (%) |
| Flow Diagram: copy and paste from the study if present, otherwise describe women<br>- enrolled,<br>- included,<br>- analysed by NIPT,<br>- analysed by comparator test<br>- analysed by reference standard |
| Patients with a result from NIPT (n/N, % on included patients) |
| Test failure (N, %) for |
| organizational reasons (specify)<br>insufficient foetal fraction<br>other (specify) |
| Mean reporting time for test's results |
| Women with NIPT result and reference standard (N, %) |
| no and % with invasive test (CVS, amniocentesis) |
| no and % with genetic test on products of conception/newborn |
| no and % with newborn exam |
| No and % of miscarriages |

| |
|---|
| INDEX TEST: diagnostic accuracy (TP, TN, FP, FN, sensitivity, specificity) |
| INDEX TEST: results on other outcomes of diagnostic accuracy (detection rate, LR etc.) |
| INDEX TEST: results on outcomes other than diagnostic accuracy (ex. impact) |
| COMPARATOR TEST: diagnostic accuracy (TP, TN, FP, FN, sensitivity, specificity) |
| COMPARATOR TEST: results on other outcomes of diagnostic accuracy (detection rate, LR etc.) |
| COMPARATOR TEST: results on outcomes other than diagnostic accuracy (ex. impact) |
| Sponsored |
| Notes |

### Selected assessment elements

Table 5 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'. In addition, assessment elements from the HTA Core Model® Applications for Screening Technologies and the HTA Core Model® Applications for Diagnostic technologies have been screened and included/merged with the existing questions if considered relevant.

**Table 5. Assessment elements and translating research questions**

| ID | Topic | Topic Issue | Relevance in this assessment Yes/No | 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 | What is non-invasive prenatal testing (NIPT) and what are the comparators? |
| B0002 | Features of the technology and comparators | What is the claimed benefit of the technology in relation to the comparator(s)? | Yes | What is the claimed benefit of NIPT in relation to the comparators? |
| B0003 | Features of the technology | What is the phase of development and implementation of the technology and the comparator(s)? | Yes | What is the phase of development and implementation of NIPT and the comparators? |
| 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 | Who administers NIPT and the comparators and in what context and level of care are they provided? |
| B0008 | Investments | What kind of special premises are | Yes | What kind of special premises are needed to use NIPT and |

| ID | Topic | Topic Issue | Relevance in this assessment Yes/No | Research question(s) or reason for non-relevance of 'mandatory' elements |
|---|---|---|---|---|
| | and tools required to use the technology | needed to use the technology and the comparator(s)? | | the comparators? |
| B0009 | Investments and tools required to use the technology | What equipment and supplies are needed to use the technology and the comparator(s)? | Yes | What equipment and supplies are needed to use NIPT and the comparators? |
| B0010 | Investments and tools required to use the technology | What kind of data/records and/or registry is needed to monitor the use of the technology and the comparators? | Yes | What kind of data/records and/or registry is needed to monitor the use of NIPT and the comparators? |
| B0012 | Investments and tools required to use the technology | What kinds of requirements in terms of qualification and quality assurance processes are needed for the use or maintenance of the technology? | Yes | What kinds of requirements in terms of qualification and quality assurance processes are needed for the use or maintenance of prenatal screening with NIPT? |
| A0020 | Regulatory Status | For which indications has the technology received marketing authorisation or CE marking? | Yes | For which indications has NIPT received marketing authorisation or CE marking? |
| A0021 | Regulatory Status | What is the reimbursement status of the technology? | Yes | What is the reimbursement status of NIPT in prenatal screening? |
| **Health problem and current use of technology** | | | | |
| A0002 | Target Condition | What is the disease or health condition in the scope of this assessment? | Yes | What are the fetal chromosome aneuploidies in the scope of this assessment? |
| A0003 | Target Condition | What are the known risk factors for the disease or health condition? | Yes | What are the known risk factors for fetal chromosome aneuploidies? |
| A0004 | Target Condition | What is the natural course of the disease or health condition? | Yes | What is the natural course of fetal chromosome aneuploidies? |
| A0005 | Target Condition | What are the symptoms and the burden of disease or health condition for the | Yes | What are the symptoms and the burden of disease of chromosome aneuploidies? |

| ID | Topic | Topic Issue | Relevance in this assessment Yes/No | Research question(s) or reason for non-relevance of 'mandatory' elements |
|---|---|---|---|---|
| | | patient? | | |
| A0006 | Target Condition | What are the consequences of the disease or health condition for the society? | Yes | What are the consequences of chromosome aneuploidies for the society? |
| A007 | Target Condition | What is the target population in this assessment? | Yes | Who is the target population for prenatal aneuploidies screening? |
| A0011 | Utilisation | How much are the technologies utilised? | Yes | How much is prenatal aneuploidies screening used and how much is NIPT utilised? |
| A0023 | Target population | How many people belong to the target population? | Yes | How many people belong to the target population for prenatal aneuploidies screening? |
| A0024 | Current Management of the Condition | How is the disease or health condition currently diagnosed according to published guidelines and in practice? | Yes | How are chromosome aneuploidies currently screened and diagnosed according to published guidelines and practice? |
| A0025 | Current Management of the Condition | How is the disease or health condition currently managed according to published guidelines and in practice? | Yes | How are chromosome aneuploidies currently managed according to published guidelines and in practice? |
| **Clinical effectiveness** | | | | |
| D0001 | Mortality | What is the expected beneficial effect of the intervention on mortality? | Yes | What is the expected beneficial effect of prenatal screening with NIPT on neonatal mortality? |
| D0005 | Morbidity | How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition? | Yes | How does prenatal screening with NIPT affect the frequency of newborns with aneuploidies? |
| D0006 | Morbidity | How does the technology affect progression (or recurrence) of the disease or health condition? | Yes | How does prenatal screening with NIPT affect progression of pregnancy? |
| D0011 | Function | What is the effect of the technology on patients' body functions? | No | NIPT is an in vitro test which has no effect on body functions |
| D0016 | Function | How does the use of technology affect activities of daily living? | No | NIPT is an in vitro test used for screening, which has no effect on activities of daily living |
| D0012 | Health-related quality of life | What is the effect of the technology on generic health-related quality of life? | Yes | What is the effect of NIPT on mothers health-related quality of life? |

| ID | Topic | Topic Issue | Relevance in this assessment Yes/No | Research question(s) or reason for non-relevance of 'mandatory' elements |
|---|---|---|---|---|
| D0017 | Patient satisfaction | Were patients satisfied with the technology? | Yes | Were patients satisfied with NIPT? |
| D0030 | Quality of life | Does the knowledge of the test result affect the patient´s non-health related quality of life? | Yes | Does the knowledge of the NIPT results affect the patient´s non-health related quality of life? |
| D0024 | Test-accuracy | What is the accuracy of the test against reference standard? | Yes | What is the accuracy of NIPT against reference standard? |
| D1002 | Test accuracy | How does the test compare to other optional tests in terms of accuracy measures? | Yes | How does NIPT screening compare to other optional screening approaches in terms of accuracy measures? |
| D1006 | Test accuracy | Does the test reliably rule in or rule out the target condition? | Yes | Does the test reliably rule in or rule out chromosome aneuploidies? |
| D1007 | Test accuracy | How does accuracy of NIPT vary in different settings? | Yes | How does accuracy of NIPT vary in different settings? |
| D0020 | Change in management | Does use of the test lead to improved detection of the condition? | Yes | Does the use of NIPT lead to improved detection of chromosome aneuploidies? |
| D0021 | Change in management | How does the test change physician´s management decisions? | Yes | How does NIPT change physician´s management decisions? |
| D0022 | Change in management decisions | Does the test detect other potential health conditions that can impact the subsequent management decisions | Yes | Does NIPT detect other potential health conditions that can impact the subsequent management decisions |
| D0010 | Change in management | How does the technology modify the need for hospitalisation? | Yes | How does the technology modify the need for hospitalisation? |
| D0029 | Benefit-harm balance | What are the overall benefits and harms of the technology in health outcomes | Yes | What are the overall benefits and harms of NIPT in health outcomes? |
| **Safety** | | | | |
| C0008 | Patient safety | How safe is the technology in relation to the comparator(s)? | Yes | How safe NIPT in relation to the comparators? |
| C0002 | Patient safety | Are the harms related to dosage or frequency of applying the technology? | No | Not relevant for in-vitro technologies |
| C0004 | Patient safety | How does the frequency or severity of harms change over time or in different settings? | No | Not relevant for in-vitro technologies |
| C0005 | Patient safety | What are the susceptible patient groups that are more likely to be harmed through the use of the technology? | No | Not relevant for in-vitro technologies |

| ID | Topic | Topic Issue | Relevance in this assessment Yes/No | Research question(s) or reason for non-relevance of 'mandatory' elements |
|---|---|---|---|---|
| C006 | Patient safety | What are the consequences of false positive, false negative and incidental findings generated by using the technology from the point of view of patient safety? | Yes | What are the consequences of false positive, false negative and incidental findings generated by using the technology from the point of view of patient safety? |
| C0007 | Patient safety | Are the technology and comparator(s) associated with user-dependent harms? | No | Not relevant for in-vitro technologies |
| 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)? | Yes | What kind of data/records and/or registry is needed to monitor the use of NIPT and the comparators? |
| **Additional assessment elements** | | | | |
| **Ethical issues** | | | | |
| F0010 | Benefit-harm balance | What are the known and estimated benefits and harms for patients when implementing or not implementing the technology | Yes | What are the known and estimated benefits and harms for pregnant woman when implementing or not implementing NIPT |
| F0011 | Benefit-harm balance | What are the benefits and harms of the technology for relatives, other patients, organisations, commercial entities, societies, etc.? | Yes | What are the benefits and harms of NIPT for relatives, other patients, organisations, commercial entities, societies, etc.? |
| F003 | Benefit-harm balance | Are there any other hidden or unintended consequences of the technology and its applications for patients, relatives, other patients, organisations, commercial entities, society, etc.? | Yes | Are there any other hidden or unintended consequences of NIPT and its applications for patients, relatives, other patients, organisations, commercial entities, society, etc.? |
| F004 | Autonomy | Does the implementation or use of the technology affect the patient´s capability and possibility to exercise autonomy? | Yes | Does the implementation or use NIPT affect the patient´s capability and possibility to exercise autonomy? |
| F006 | Autonomy | Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used? | Yes | Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used? |
| F0101 | Respect for persons | Does the technology invade the sphere of the patient/user? | Yes | Does NIPT invade the sphere of the patient/user? |
| F0012 | Justice and | How does implementation or withdrawal | Yes | How does implementation or withdrawal of the technology |

| ID | Topic | Topic Issue | Relevance in this assessment Yes/No | Research question(s) or reason for non-relevance of 'mandatory' elements |
|---|---|---|---|---|
| | Equity | of the technology affect the distribution of resources | | affect the distribution of resources |
| F0017 | Ethical consequences of the HTA | What are the ethical consequences of the choice of endpoints, cut off-values and comparators/controls in the assessment? | Yes | What are the ethical consequences of the choice of endpoints, cut off-values and comparators/controls in the assessment? |
| **Organisational issues** | | | | |
| G0001 | Health delivery system | How does the technology affect the current work processes? | Yes | How does NIPT affect the current work processes? |
| G0003 | Health delivery process | What kind of process ensures proper education and training of staff? | Yes | What kind of process ensures proper education and training of staff? |
| G0004 | Health delivery process | What kind of co-operation and communication of activities have to mobilised | Yes | What kind of co-operation and communication of activities have to mobilised |
| G0012 | Health delivery process | In what way is the quality assurance and monitoring system of the new technology organised? | Yes | In what way is the quality assurance and monitoring system of NIPT organised? |
| G0005 | Structure of health care system | How do de-centralisation or centralisation requirements influence the implementation of the technology? | Yes | How do de-centralisation or centralisation requirements influence the implementation of NIPT? |
| G0006 | Process related costs | What are the costs of processes related to acquisition and setting up the new technology? | Yes | What are the costs of processes related to acquisition and setting up NIPT? |
| G0023 | Process related costs | How does the technology modify the need for other technologies and use of other resources? | Yes | How does NIPT modify the need for other technologies and use of other resources? |
| G0007 | Process related costs | What are the likely budget impacts of implementing the technologies being compared? | Yes | What are the likely budget impact of implementing the technologies being compared? |
| G0008 | Management | What management problems and opportunities are attached to the technology? | Yes | What management problems and opportunities are attached to NIPT? |
| G0009 | Management | Who decides which people are eligible for the technology and on what basis? | Yes | Who decides which people are eligible for NIPT and on what basis? |
| G0010 | Culture | How is the technology accepted? | Yes | How is NIPT accepted? |
| G0011 | Culture | How are other interest groups taken into account in the | Yes | How are other interest groups taken into account in the planning/implementation of NIPT? |

| ID | Topic | Topic Issue | Relevance in this assessment Yes/No | Research question(s) or reason for non-relevance of 'mandatory' elements |
|---|---|---|---|---|
| | | planning/implementation of the technology? | | |
| **Patients and social aspects** | | | | |
| H0100 | Patients perspectives | What expectations and wishes do patients have with regard to the technology and what do they expect to gain from the technology? | Yes | What expectations and wishes do patients have with regard to NIPT and what do they expect to gain form the technology? |
| H0006 | Patients perspectives | How do patients perceive the technology under assessment? | Yes | How do patients perceive NIPT? |
| H0012 | Social group aspects | Are there factors that could prevent a group or person from gaining access to the technology? | Yes | Are there factors that could prevent a group or person from gaining access to NIPT? |
| H0202 | Communication aspects | How are treatment choices explained to the patients | Yes | How are screening options explained to the patients? |
| H0203 | Communication aspects | What specific issues may need to be communicated to patients to improve adherence | Yes | What specific issues may need to be communicated to patients to improve adherence |

**Checklist for patient and social aspects**

The following checklist should be considered in order to determine whether there are specific ethical, organisational, social and legal aspects which also need to be addressed. Since the assessment is comparative in nature, only new issues should be dealt with, which arise from a difference between the technology to be assessed and its major comparator(s). Already known problems/issues with regard to ethical, organisational, social and legal aspects which are common to the technology to be assessed and its comparator(s) will, as a rule, not be addressed, as it is not to be expected that the addition of a new technology will lead to changes.
If a question is answered with 'yes', further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further.

Table 6. 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 |

  

| | |
|---|---|
| Routine introduction of NIPT for prenatal genetic screening, could lead to changes in the risk managing approach of pregnant women, which may cause ethical issues for the couple as well as for the health-care provider, as benefits/risks could be substantially different and must be carefully explained. | |
| 1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant? | Yes |
| Prenatal genetic screening NIPT testing can be offered to women with different risks of developing fetal aneuploides, leading to important ethical considerations, NIPT testing could create a great demand that is probably not justified on health grounds in some risk groups. | |
| 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 |
| The new intervention could require important organisational changes if NIPT is implemented in hospital premises and centralised to tertiary care units. Even if the samples are sent to external clinical labs, organisational changes might be required to ensure that there are no delays and an important budget impact can be expected. | |
| 2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant? | Yes |
| NIPT could replace other screening tests and lead to a change in the current pathways of care, affecting the work load at different levels (reduce imaging, amniocentesis, etc.) | |
| 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 social issues? | Yes |
| NIPT are being offered as accurate tests which could avoid invasive testing, and this could have led to great expectations regarding their application, leading to a non-justified demand in some groups. Pressure can also be imposed on parents to avoid a child with anomalies and lead to possible discrimination of people with anomalies. | |

| | |
|---|---|
| 3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant? | Yes |
| | |
| 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 |
| | |

# 5.0 ORGANISATION OF THE WORK

## 5.1 MILESTONES AND DELIVERABLE(S)

Table 7. Milestones and Deliverables

| **Milestones/Deliverables** | **Start date** | **End date** |
|---|---|---|
| **Project duration** | **[01/11/2016]** | **[30/01/2018]** |
| **Scoping phase** | **[01/11/2016]** | **[05/04/2017]** |
| Identification of manufacturer (s) | [01/11/2016] | [10/11/2016] |
| Send request for draft Submission file template to manufacturer(s) | [11/11/2016] | [25/11/2016] |
| Scoping and development of draft Project Plan | [01/11/2016] | [09/12/2016] |
| Internal Scoping SABA e-meeting (author (s), co-author (s), dedicated reviewer (s) and external reviewer (s)-if identified by then) | [12/12/2016] | [19/12/2016] |

| | | |
|---|---|---|
| Amendment of draft Project Plan | [20/12/2017] | [7/02/2017) |
| Consultation of draft Project Plan with dedicated reviewers | [7/02/2017] | [14/02/2017] |
| Consultation of draft Project Plan with stakeholders (external expert and manufacturers) | 07/02//2017 | 14/02/2017 |
| Amendment of draft Project Plan and final Project Plan available | [14/02/2017] | [22/03/2017] |
| Completion of Submission file template by manufacturer(s) | [25/11/2016] | [22/02/2017] |
| Clarifying further questions concerning draft Submission file | [22/02/2017] | [03/02/2017] |
| Final submission file | [03/02/2017] | [05/04/2017] |
| **Assessment phase** | **[22/03/2017]** | **[31/01/2018]** |
| Writing first draft rapid assessment | [05/04/0217] | [31/07/2017] |
| Review by pool of ≥2 dedicated reviewers | [18/09/2017] | [2/10/2017] |
| Writing second draft rapid assessment | [3/10/2017] | [31/10/2017] |
| Review by ≥ 2 external clinical experts and by other potential stakeholders | [1/11/2017] | [21/11/2017] |
| Writing third draft rapid assessment | [22/11/2017] | [12/12/2017] |
| Medical editing | [12/12/2017] | [19/12/2017] |
| Writing of final version of rapid assessment | [8/01/2018] | [22/01/2018] |
| Formatting | [23/01/2018] | [30/01/2018] |
| Final version of REA | | **[week** from **30/01/2018** - to 05/02/2018] |

## 5.2 MEETINGS

A SABA e-meeting will be held with the pilot team during the Scoping phase (16/12/2016). Whenever needed, further e-meetings can be scheduled.

## 6.0 COMMUNICATION

**Table 8. Communication**

| Communication Type | Description | Date | Format | Participants/ Distribution |
|---|---|---|---|---|
| **Scoping** | *To discuss and reach the consensus on the scoping, as a preparation for the final Project Plan (optional).* | [19/12/2016] | E- SABA meeting | Author(s), co-author(s), dedicated reviewers, CT |
| ***Feedback on draft submission file (optional)*** | *To formulate clarifying questions on draft submission file before sending it to the manufacturers* | [23/12/2016] | E-mail | Authors (s), co-authors (s), CT |

| | | | | |
|---|---|---|---|---|
| | *To point out the requirements for the final submission file by manufacturers* | [25/11/2016] | E-mail | CT, manufacturers |
| **Draft Project Plan with timelines** | Review of methods and assessment elements chosen, discussion of time-lines | [16/12/2016] | E-mail | Author(s), Co-author(s), dedicated reviewer(s), CT |
| **Final Project Plan** | Review of methods and assessment elements chosen, discussion of time-lines. | [22/03/2017] | E-mail | Author(s), Co-author(s), dedicated reviewers, CT |
| **First draft of the rapid assessment** | To be reviewed by dedicated reviewer(s) | [18/09/2017] | E-mail | Dedicated reviewer(s) |
| | To discuss comments of dedicated reviewers (optional) | [03/10/2017] | E-Mail (e-meetings to be planned here -optional) | Author(s), co-author(s), dedicated reviewers |
| **Second draft of the rapid assessment** | To be consulted with ≥2 clinical expert (other potential stakeholders) | [01/11/2017] | E-mail | ≥2 clinical experts (other potential stakeholders) |
| **Final rapid assessment** | Medical editing by external editor | [12/12/2017] | E-Mail | Medical Editor |

## 6.1 DISSEMINATION PLAN

The final rapid assessment will be distributed as laid-out in the Work Plan of WP4.

## 7.0 COLLABORATION WITH STAKEHOLDERS

The 2nd draft version of the assessment will be reviewed by external experts (and other potential stakeholders).
Manufacturers will fill in the submission file, check the draft for accuracy and will be contacted with regard to questions if necessary.

## 8.0 COLLABORATION WITH EUnetHTA WPs

For the individual rapid assessment, no collaboration with other WPs is planned.

## 9.0 RESOURCE PLANNING

Please estimate the expected input in terms of human and financial resources necessary to achieve the project objectives.

## 9.1 HUMAN RESOURCES

**Table 9. Human resources**

| **Role** | **Total number of person days** | **Source** | |
|---|---|---|---|
| | | **Staff of participating organisations** | **Subcontracting** |

  

| | | | |
|---|---|---|---|
| **Author** | 80 person days | 80 person days | - |
| **Co-Author** | 25 person days | 25 person days | - |
| **Reviewer** | 5 person days each | 5 person days each | - |
| **External expert** | 5 person days each | - | - |
| **Medical Editor** | 10 person days | - | 10 person days |
| **Layout** | 5 person days | - | 5 person days |

## 10.0 CONFLICT OF INTEREST MANAGEMENT

Conflicts of interest will be handled according to EUnetHTA JA2 Conflict of Interest Policy. As conflict of interest may be topic dependent, conflict of interest declarations will be collected from authors and reviewers involved in a specific assessment via the Declaration of interest and confidentiality undertaking (DOICU) form. Authors and reviewers who declare a conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other assessments.
If external experts are involved in WP4 a conflict of interest declaration will be collected from them regarding the topic. External experts who declare a conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other assessments.

## 11.0 EXPECTED OUTCOME(S)

Please briefly describe the expected project outcomes, i.e., changes that occur as a result of the project when the objectives are reached.

| **Project outcome(s)** |
|---|
| Collaborative assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of non-pharmaceutical health technologies will have been produced. These assessments will have been used in the national/local context. Production processes for collaborative assessment reports will have been refined based on lessons learned and experiences from JA2. The decentralized approach for producing collaborative assessments will have been probed. The implementation of collaborative assessments in the national/local context will have been facilitated. |

# C. REFERENCES

[1] Wilson KL, Czerwinski JL, Hoskovec JM, Noblin SJ, Sullivan CM, Harbison A, Campion MW, Devary K, Devers P, Singletary CN. NSGC practice guideline: prenatal screening and diagnostic testing options for chromosome aneuploidy. J Genet Couns. 2013 Feb;22(1):4-15

[2] ACOG Committee on Practice Bulletins. ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. Obstet Gynecol. 2007 Jan;109(1):217-27. PubMed PMID: 17197615.

[3] Benn P, Borrell A, Chiu RW, Cuckle H, Dugoff L, Faas B, Gross S, Huang T,Johnson J, Maymon R, Norton M, Odibo A, Schielen P, Spencer K, Wright D, Yaron Y. Position statement from the Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. Prenat Diagn. 2015 Aug;35(8):725-34.

[4] Committee Opinion No. 640: Cell-Free DNA Screening for Fetal Aneuploidy. Obstet Gynecol. 2015 Sep;126(3): e31-7.

[5] Benn P, Borrell A, Chiu RW, Cuckle H, Dugoff L, Faas B, Gross S, Huang T, Johnson J, Maymon R, Norton M, Odibo A, Schielen P, Spencer K, Wright D, Yaron Y. Position statement from the Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. Prenat Diagn. 2015 Aug;35(8):725-34.

[6] European Network for Health Technology Assessment (EUnetHTA). Comparators & Comparisons. Criteria for the choice of the most appropriate comparator(s). Summary of current policies and best practice recommendations [Internet]. Copenhagen: EUnetHTA. Available from: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Choice_of_comparator.pdf.

[7] EUnetHTA guidelines. Available from: http://www.eunethta.eu/eunethta-guidelines

[8] EUnetHTA Joint Action 2 Work Package 5. The HTA Core Model for Rapid Relative Effectiveness Assessment. Version 4.2 [Internet]. Copenhage: EUnetHTA; 2015. Available from: http://meka.thl.fi/htacore/model/HTACoreModel_ForRapidREAs4.2.pdf.

[9] EUnetHTA Joint Action 2, Work Package 8. HTA Core Model ® version 3.0 (Pdf); 2016. Available from: www.htacoremodel.info/BrowseModel.aspx.

[10] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36.

[9] Cochrane Collaboration risk of bias tool (RoB 2.0 tool). Available from: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool

[11] Risk of Bias in non-randomized of Interventions (ROBINS-I tool). Available from: https://sites.google.com/site/riskofbiastool/welcome/home

[12] The GRADE working group. GRADE guidelines - best practices using the GRADE framework [Internet]; 2013. Available from: http://www.gradeworkinggroup.org/publications/JCE_series.htm.

  

[13] CASP UK. CASP Checklist. 10 questions to help you make sense of qualitative research [Internet]. Oxford: CASP UK; 2013. Available from: http://media.wix.com/ugd/dded87_29c5b002d993 42f788c6ac670e49f274.pdf.

[14] Lewin S, Glenton C, Munthe-Kaas H, Carlsen B, Colvin CJ, Gülmezoglu M, et al. Using Qualitative Evidence in Decision Making for Health and Social Interventions: An Approach to Assess Confidence in Findings from Qualitative Evidence Syntheses (GRADE-CERQual). PLoS Med. 2015;12(10): e1001895.

  