

15 | 09 | 2019

VALUE-Dx



Challenges of diagnostics

There is a dearth of studies which can provide the evidence of the value of diagnostics in well-characterised situations, and the lack of such evidence has been a hindrance for diagnostic innovation.

The current diagnostic business model - focused on technology used, lab activity measures, and complexity indicators – is antiquated.

The current financial framework (i.e. inadequate reimbursement, reimbursement based on technology rather than medical value) does not encourage innovation related to diagnostic tests.

Regulatory approval has historically been based on analytical performance, rather than on clinical effectiveness.

Psychological, social, economical, ethical, organisational barriers prevent the uptake and development of diagnostics for antimicrobial stewardship.

Vision & Purpose

Our vision is to transform clinical practice, improve patient outcomes, and combat AMR, through the widespread use of clinical and cost-effective innovative diagnostics strategies to achieve more personalised, evidence-based antibiotic prescription and use in community care settings.

Our purpose is to facilitate and accelerate the rigorous assessment and implementation of (new) diagnostic technologies into healthcare settings, by establishing the infrastructure, methods, processes and approaches needed to understand, evaluate, assess, and demonstrate the multi-faceted value of diagnostics and overcome the associated barriers to their widespread adoption and use.

Our focus is on realising its vision and purpose on community-acquired acute respiratory tract infections (CA-ARTI).

Therefore, VALUE-Dx will focus on diagnostic strategies relevant to reducing AMR in CA-ARTI in community care settings, referred to as “CA-ARTI-Dx”

Community Care Settings

- As required by the call topic, VALUE-Dx will focus its research on community care, which is defined as the first point of contact with health services.
- This includes both in and out of office hours care.
- **Settings:** general practice, urgent care centres, accident and emergency rooms and other acute services in hospitals, paediatric care centres, and rehabilitation and long-term care facilities.

Objectives of VALUE-Dx

Helping to build the economic case for rapid diagnostics as a public good in the fight against AMR

1. To **design a health-economic framework (HEF)** to assess and demonstrate the value of diagnostics both for individual patients and for public health impact by reducing antibiotic use and subsequent antibiotic resistance among patients.

2. To **establish a sustainable European Standardised Care Network** adequately trained and resourced to conduct clinical trials evaluating the value of diagnostics.

3. To **design and implement clinical studies to demonstrate the value of diagnostics** in the optimal management of Community-Acquired Acute Respiratory Tract Infections (CA-ARTIs)

4. To **explore, define and attempt to resolve the psychological, ethical and social barriers** which prevent the more widespread adoption of diagnostics delivering healthcare to the population.

The VALUE-Dx Consortium



UNIVERSITÀ
di VERONA



University Medical Center Groningen



RAMBAM
Health Care Campus



NICE National Institute for
Health and Care Excellence

Gesundheit Österreich
GmbH



Contribution from European Commission, Wellcome, and IVD Companies

Budget overview

Total budget VALUE-
Dx:
€ 13,643,431

European Commission:
€ 6,799,100

Wellcome:
€ 3,400,000

IVD companies:
€ 3,444,331
In kind contribution:
€ 2,939,331
In cash contribution:
€ 505,000

GOVERNANCE

GENERAL ASSEMBLY (VALUE-Dx Partners) EFPIA partners, IMI-JU Associated Partners, Beneficiaries

Executive Board (VALUE-Dx WP Co-Leads)

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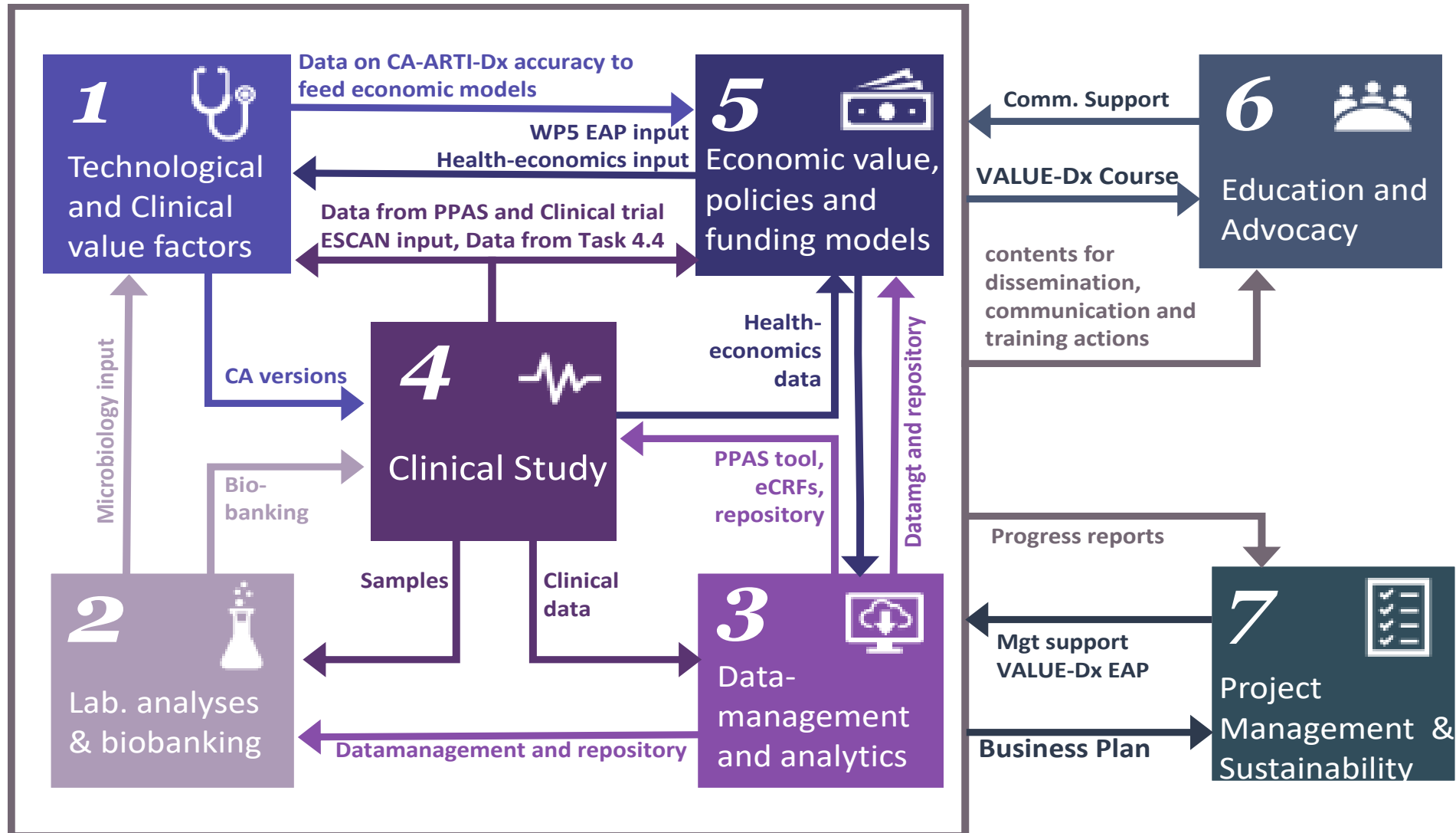


Murat Akova
ESCMID

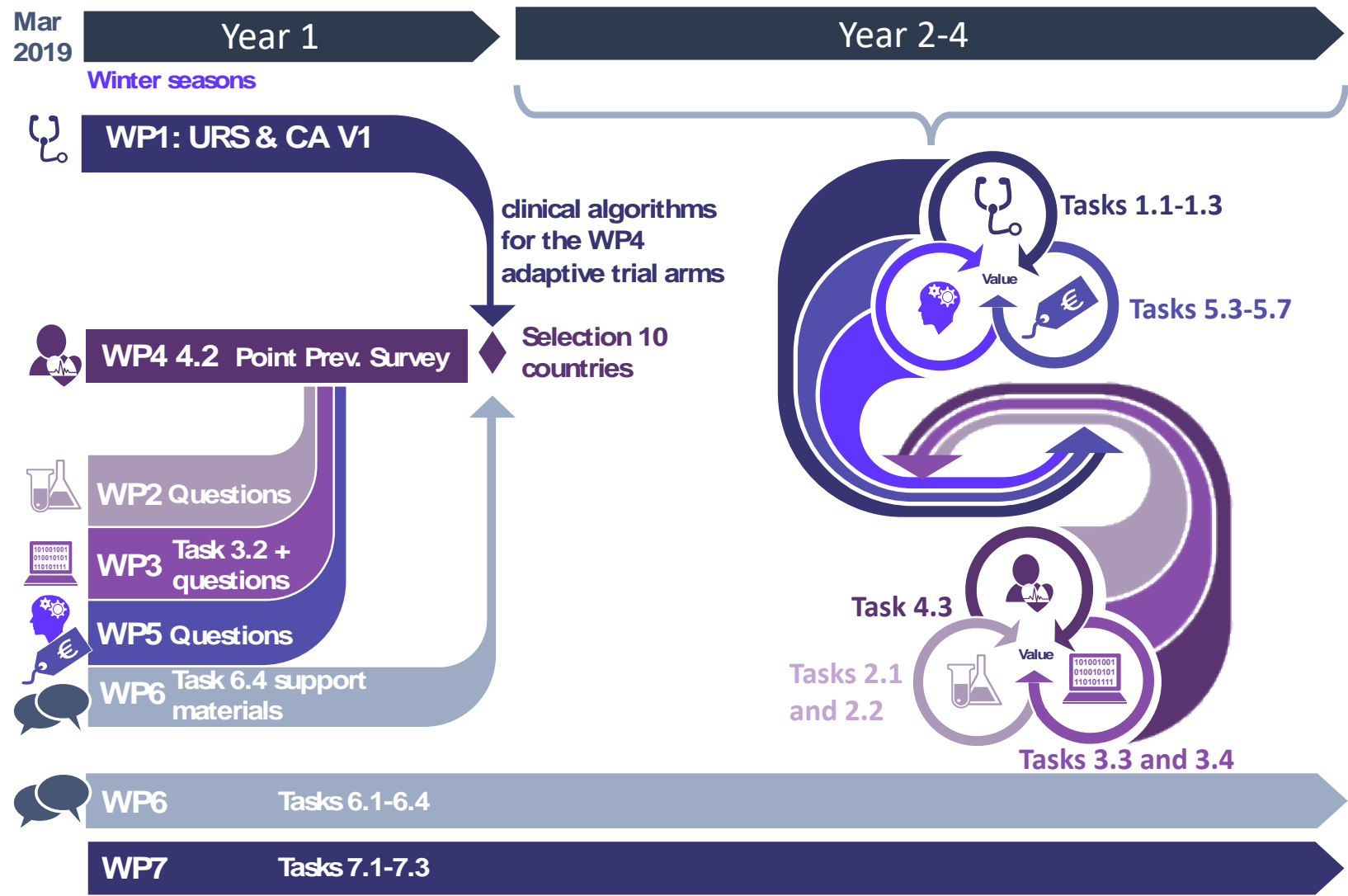


Renuka Gadde
Becton Dickinson

Interaction between the Work Packages



Gantt Chart



Access to Clinical Trial Networks



Primary care

>200 primary care practises in >20 European countries



- ✓ Recruited over 20,000 patients into clinical studies on ARTI in GRACE and other studies.
- ✓ Randomised 3,268 participants in a response-adaptive platform trial of a drug for a CA-ARTI in PREPARE.

Chris Butler



Hospital care + Labs

>900 hospitals and >800 labs in >40 European countries



- ✓ COMBACTE projects are managing >20 trials, including phase I – III trials for many new compounds against multi-resistant bacteria, and recruited over 20,000 patients.

Marc Bonten (CLIN-Net)

Herman Goossens (LAB-Net)



Paediatric care

90 paediatric clinical sites in 18 countries



- ✓ Network of hospital sites of neonates and children.
- ✓ Active a.o in ZIKACTION, PREPARE, C4C (IMI-2)

Carlo Giaquinto



Long Term Care

Nursing homes and rehabilitation centres in 11 countries in Europe and Israel with more than 14,000 LTCF beds

- ✓ Experience in clinical trials on antibiotic use, influenza epidemiology and vaccines, microbiome and more.

Evelina Tacconelli
Mical Paul



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Work Packages

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Evelina **Tacsonelli** Jorge **Villacian**

WP1

Technological & Clinical Value Factors



Objectives

1. To **develop evidence-based clinical algorithms** for CA-ARTI and assess the diagnostic accuracy and the clinical utility of POCT for specific groups of patients, clinical findings, and settings;
2. To **develop evidence-based URS's** to support future development and implementation of rapid diagnostics to reduce AMR for CA-ARTI, and to refine the methods and processes to make them applicable to point of care diagnostic developments for other infectious disease indications);
3. To **create a technological roadmap** that incorporates recommendations for short- and long-term goals to help companies and research institutions prioritize investment decisions in the field of CA-ARTI-Dx.

Tasks

Task 1.1 Develop Clinical Algorithms

(**UNIVR**; FIND, UA, UEDIN, UMCU, UMCG, PENTA, RAMBAM, UNIRIOJA, UOXF, bMx, Janssen, BD, Accelerate)

Task 1.2 Develop User Requirement Specifications (URS)

(**UEDIN**; FIND, UA, UMCU, UMCG, PENTA, RAMBAM, UNIRIOJA, UOXF, UNIVR, bMx, Janssen, BD, Accelerate)

Task 1.3 Develop technological roadmap

(**UEDIN**; UMCG, UA, bMx, Janssen, Accelerate)

Task 1.1 Develop Clinical Algorithms

Three stages:

1. Systematic reviews of existing evidence for the use of diagnostics for CA-ARTI (M12, first version of algorithm to be sent to WP4);
2. Integration of data from the **Point Prevalence Audit Study** planned in WP4 and **stakeholders' consultation** (M18, second version);
3. Integration of the results from the **clinical trials** in WP4 (M48, final version).

Task 1.1 Develop Clinical Algorithms

1. **Systematic reviews** of existing evidence for the use of diagnostics for CA-ARTI (M12, first version of algorithm to be sent to WP4):

- Identify and appraise evidence on sensitivity, specificity, accuracy and predictive values of patients' signs and symptoms and diagnostic tests, based on published and unpublished (e.g. GRACE, PREPARE, FIND) data;
- Assess the effectiveness of diagnostic tests or diagnostic strategies on patients' relevant outcomes;
- Integrate radiologic and biomarkers to determine;
- Determine optimal time point in the care pathway to perform the diagnostic test for CA-ARTI and on which populations testing will give greatest added value using PICO questions (Problem/Patient, Intervention, Comparison, Outcome)

Quality assessment: GRADE approach (Cochrane methodology used to summarise the quality of evidence)

Synthesis of quantitative variables: meta-analysis where possible and appropriate, pooling the estimates of outcomes using random-effects models.

Task 1.1 Develop Clinical Algorithms

1. **Systematic reviews** of existing evidence for the use of diagnostics for CA-ARTI (M12, first version of algorithm to be sent to WP4):

Analysis of results by means of two supervised **Machine Learning (ML)** methods: **Support Vector Machines (SVM)** and **Random Forest (RF)**.

Computation will be performed with the scikit-learn Python package and feature importance will be computed with R programming language using the RF package. Performance of classifiers will be evaluated with area under the receiver operating characteristic curve and analysis of the confusion matrix. The out-of-bag accuracy of RF will be monitored to determine the required number of trees. Data will be stored in a MongoDB Atlas database and parsed with Python programming language. Each patient will be encoded with a normalised numerical vector representing the patient's symptoms, radiological findings and diagnostic tests, which will be encoded according to sensitivity and specificity. Different feature selection approaches will be tested by type of population and settings.

Task 1.1 Develop Clinical Algorithms

2. Integration of data from the **Point Prevalence Audit Study** planned in WP4 and **stakeholders' consultation** (M18, second version of algorithm):

To define the feasibility of the clinical algorithms in daily practice, experts, representatives from different settings (general practitioners, medical doctors for LTCFs and emergency departments) in the VALUE-Dx EAP and WP4 members, will **weigh the criteria** using a preferences online survey based on applying the **PAPRIKA** (Potentially All Pairwise Rankings of all possible Alternatives) method.

The selection process of the external experts will be performed in the attempt of balancing different geographic origin, gender and expertise.

Task 1.1 Develop Clinical Algorithms

3. Integration of the results from the **clinical trials** in WP4 (M48, final version of algorithm):

The final deliverable D1.1 will report all clinical algorithms validated in the trials according to the countries, settings, and populations included in the clinical trials.

Task 1.1 Develop Clinical Algorithms – Different steps

Definition of criteria to include in the evidence based literature search



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graph TD; A[Definition of criteria to include in the evidence based literature search] --> B[Extraction of evidence for all criteria]; B --> C["Evidence ranking and development of clinical algorithms (Machine Learning) (First version CA; M12)"]; C --> D["First validation through Experts and Stakeholders' survey (PAPRIKA method) (second version CA; M18)"]; D --> E["Second validation through clinical trials performed in WP4 (Final version CA; M48)"];
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Extraction of evidence for all criteria

Evidence ranking and development of clinical algorithms
(Machine Learning) (First version CA; M12)

First validation through Experts and Stakeholders' survey
(PAPRIKA method) (second version CA; M18)

Second validation through clinical trials performed in WP4
(Final version CA; M48)

Machine Learning and PAPRIKA Methodologies

ADVANTAGES

1. Clinical algorithms can be easily updated with new data as soon as available from WP2 (prevalence of etiology) and WP4 (sensitivity/specificity of a diagnostic test; prevalence of clinical symptoms).
2. Allows sustainability (future constant update with new evidence).
3. Can be applied to other clinical syndromes.

Task 1.2 User Requirement Specifications

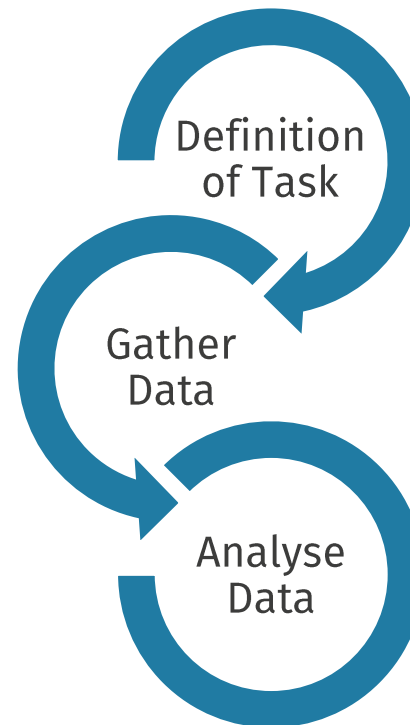
User Requirement Specification (URS) Document

Lists User Requirements (e.g. time to result)

Rates User Requirements (optimal, minimum)

Informs technical development and implementation

⇒ Target Product Profile (TPP),
Product Development Plan (PDP)



- **User** patient, medical doctor, nurse, pharmacist or other
- **Settings** physician's office, ED of hospitals, paramedical clinics, long term care facilities, nursing homes, rehabilitation centres)
- **Populations** children, targeted comorbidities, immunosuppressive therapy, transplants, neoplastic patients
- **Criteria** current practise and perceived unmet need, indented use, test and test procedure, test performance, use of results

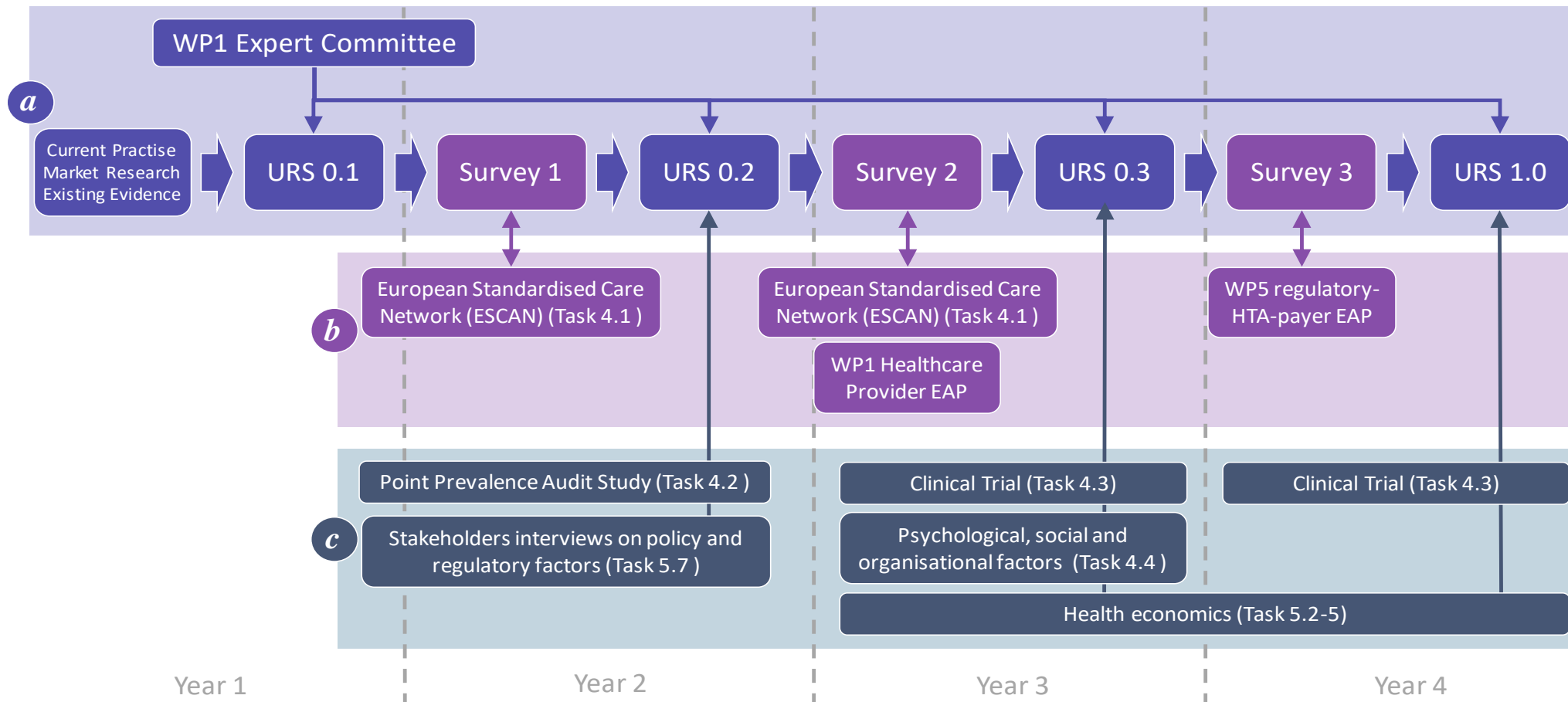
Task 1.2 User Requirement Specifications

For the URS we will collate, curate and publish data and (optimal, minimum) criteria around rapid diagnostic tests including but not limited to:

- Current practice and perceived unmet need;
- Intended use (test location, position in patient care pathway, user, screening/monitoring/diagnosis, qualitative/quantitative results, specimen preparation, target population, use of data, compliant local rules and regulations);
- Test and test procedure (price per test, equipment, components, reagents, assay steps, turnaround time/time to result, precautions, use of third party components (e.g. swabs), storage conditions, connectivity with clinical record);
- In collaboration with WP2 and WP4, test performance (sensitivity, specificity, positive/negative predictive value, shelf life, reproducibility (incl. near clinical threshold and in real clinical settings)), and use of results (positive/negative, clinical significance, impact on patient care/antibiotic choice, care costs).

Task 1.2 User Requirement Specifications

Schematic of Delphi-like process of Task 1.2 with structured feed-back including (a) sequential roadmap development, (b) involved internal and external stakeholder groups and (c) input from WP4 and 5.



Task 1.3 Technological Road Map

Aims:

- Provide recommendations for future development, implementation, and increased uptake of CA-ARTI-Dx;
- Define short-term and long-term goals and provide key information to help diagnostic innovators and funders prioritize investment decisions;
- Consider the (bio)assay content as well as the technical device/instrument gaps;
- Highlight current unmet needs and shortcomings of the available diagnostic solutions.

Methodology: the GOTChA (Goals, Objectives, Technical Challenges, Approaches) to determine which emerging technologies hold the most promise:

- Evidence from systematic reviews;
- Expert consultations;
- Input from other WPs;
- Interactive workshops.

Task 1.3 Technological Road Map

Kick-off Workshop: M2

- Involving ND4ID PhD students (= annual ND4ID status seminar), and their supervisors (= members of the WP1 EAP and WP1 Expert Committee);
- To map the current diagnostic field including major development programmes as well as availability and regulatory status of rapid tests;
- In collaboration with the work on mapping of diagnostic tools to address AMR coordinated by WHO and funded by the Wellcome Trust;
- Utilize data from systematic reviews to develop clinical algorithms and URS and of the regulatory, economic and geographical situation sourcing from WP5.

Workshop 1: M14

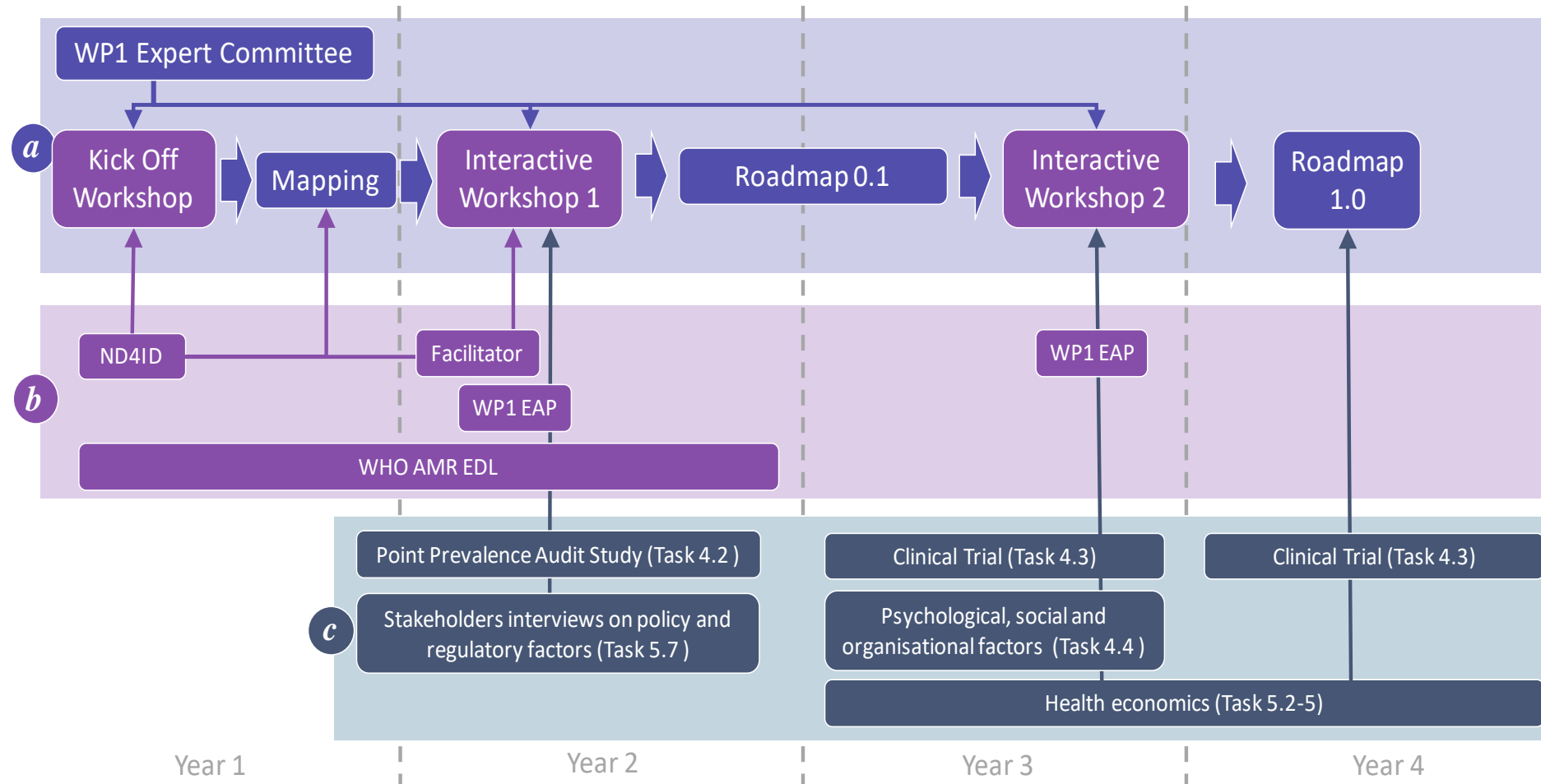
- Involving the ND4ID PhD students and their supervisors, selected members of the VALUE-Dx EAPs and additional experts;
- Leading to first roadmap draft 0.1.

Workshop 2: M36

- Utilizing evidence as generated in WP4 and 5;
- Leading to final Roadmap 1.0.

Task 1.2 Technological Road Map

Schematic process of Task 1.3 including (a) sequential roadmap development, (b) involved internal and external stakeholder groups and (c) input from WP4 and 5. Timelines not to scale



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Chris **Butler** Suzanne **Emmerich**

WP4

Clinical Study



Objectives

1. To **further develop, coordinate and manage a sustainable European Standardised Care Network (ESCAN)** with broad European coverage providing access to a large population suffering from CA-ARTI across all age groups and different community care settings, differing antimicrobial stewardship programs, country level income and differing levels of outpatient antibiotic use.
2. To **generate clinical evidence about current care and the potential value of clinical algorithms** that include one or more CA-ARTI-Dx by benchmarking current clinical practice for CA-ARTI in 20 EU Member states and H2020 Associated Countries selected from our existing COMBACTE, PREPARE, PENTA-ID and LOTTA-Net networks and enhanced with further networks, on the basis of levels of income, variation in antibiotic stewardship programs, and levels of antibiotic prescribing.
3. To **design and implement a novel, robust, flexible and efficient randomised controlled trial** of the clinical and cost-effectiveness of algorithms including one or more CA-ARTI-Dx for managing CA-ARTI in community care in 10 EU Member States and H2020 Associated Countries (selected on the basis of the results of the point prevalence audit survey; PPAS).

Tasks

Task 4.1 Coordinate the network of well-defined community care settings

(UA; UMCU, UOXF, PENTA, UNIVR, RAMBAM)

Task 4.2 Point Prevalence Audit Study (PPAS) of the presentation and management of CA-ARTI in the ESCAN

(UOXF; UMCU, UA, PENTA, UNIVR, RAMBAM, bMx, Alere, BD, Accelerate, Janssen)

Task 4.3 Clinical Trial

(UOXF; UMCU, UA, PENTA, UNIVR, RAMBAM, BERRY, bMx, Alere, BD, Accelerate, Janssen)

Task 4.4 Psychological, social and organisational factors & Process evaluation

(UOXF, UA; bMx)

WP4 Clinical Study

WP4 will consist of two clinical studies:

1. **A two-week long point prevalence audit study** on the management of CA-ARTI in 20 EU Member States and H2020 Associated Countries. Information feeds into WP1 clinical algorithm development and WP5 economic modelling studies, and be used as the basis for selection of sites for the trial implementation.
2. **A response adaptive platform clinical trial that will:**
 - Evaluate the impact of the use of clinical diagnostic strategies that include (combinations of) “host-based” and “pathogen-based” CA-ARTI-Dx on antimicrobial prescribing rates and on the course of disease;
 - Evaluate the defined measurable clinical outcome and success parameters (clinical utility) derived from WP1;
 - Use data and samples generated in the trial to determine the analytic and diagnostic performance of CA-ARTI-Dx in different settings;
 - Evaluate and test the implementation process for clinical algorithms including new diagnostic devices (change management and sustainability) as derived from WP1;
 - Explore and define the psychological, social and organisational factors influencing the widespread adoption of clinical algorithms by health care professionals in primary care, long term care facilities and emergency rooms and patients across multiple EU countries;
 - Conduct a process evaluation to assess how clinical algorithms are implemented in multiple, international community health care contexts;
 - Evaluate the health economic model(s) as derived from WP5, including cost effectiveness;
 - Implement a system for collecting, monitoring and validating measurable/data as set out above including generating clinical samples from well characterised patients for the purposes of evaluating the outcomes of the clinical trial but also for biobanking and for proof of principle studies (WP2);
 - Periodically report the status, results to date and progress to the consortium.

WP4 Clinical Study

Two-week long Point Prevalence Audit Study (PPAS)

In the winter of 2019-2020: A two-week long point prevalence audit study (PPAS) on the community management of CA-ARTI will benchmark the case-mix and management, including investigations used and antibiotic prescribing of patients consulting in 20 EU Member States and H2020 Associated Countries.

We will obtain data from community care settings.

Information will feed into the second version of the WP1 clinical algorithm and WP5 economic modelling studies and used as the basis for selection of sites for the trial implementation.

Target patient population: CA-ARTI

Community-acquired acute respiratory tract infection (CA-ARTI)

- Distinguishing upper from lower RTI virtually impossible (the term 'respiratory tract illness' has been proposed)
- Acute cough will be the dominant symptom: it is commonest acute presentation in health care where testing will have the greatest reach and impact
- Otitis media: common in children and blood tests unlikely to reduce diagnostic uncertainty
- Diagnostic may be useful in sinusitis (ruling out need for antibiotic)
- Our trial design enables us to pre-specify subgroups (e.g. infection types/sites) and prospectively power the trial for benefit or otherwise in each subgroup (rather than do usually underpowered post hoc analyses common in traditional trial designs)
- Power is based on Bayesian statistics with numerous simulations done before the trial opens to set the performance characteristics of the trial

Response adaptive platform trial

Trial identifier

Platform randomised controlled trial of point of care diagnostics for enhancing the quality of antibiotic prescribing for community acquired acute respiratory tract infection (CA-ARTI) in community care in Europe (Prudence)

Trial design

Novel, response-adaptive platform trial. The trial will be a diagnostic strategy intervention study to evaluate the use of a clinical algorithm that includes a CA-ARTI-Dx compared to care without the addition of a CA-ARTI-Dx and/or alternative diagnostic strategies using different CA-ARTI-Dx. The trial may therefore have several arms, with staggered usage as the data emerges and new algorithms are developed. We will be able to drop arms as soon as they are proven to meet (or not meet) pre-specified thresholds for effectiveness or non-effectiveness and add in new arms during the course of the trial (platform trial). The proportion of participants allocated to trial arms may be altered at pre-specified assessment points in response to emerging trial outcomes against predetermined criteria about precision to enhance study efficiency (response adaptation).

Timing

Winters of 2020/2021 and 2021/22.

Setting

Ten EU Member States and H2020 Associated Countries, to include countries with high, medium and low antibiotic use. Sites will be selected based on data generated from the point prevalence audit survey and the specification to cover a range of antibiotic prescribing levels, and country income parameters. Community Care settings will be any service that is the first point of call for patients seeking help for the CA-ARTI, including general practice, accident and emergency units, primary care paediatricians and physicians, Long-term Care Facilities and primary care nurses offering acute care to outpatients.

Response adaptive platform trial

Setting	Ten EU Member States and H2020 Associated Countries, to include countries with high, medium and low antibiotic use, and with a range of country level income and antibiotic stewardship programs. Sites will be selected based on data generated from the point prevalence audit survey in task 4.2 and the specification to cover a range of antibiotic prescribing levels, and country income parameters.
Eligibility	Patients aged one year and older with an acute or worsened cough (≤ 28 days duration) as the main symptom, or any clinical presentation considered to be caused by CA-ARTI, and consulting for the first time for this illness episode. Some of the interventions will be evaluated only in certain populations, for example according to age group and community care setting.
Initial intervention strategies	Clinical algorithms will be compared to care without a CA-ARTI-Dx. Tests to be evaluated will include host based and/or pathogen-based CA-ARTI-Dx. More than one clinical algorithm including CA-ARTI-Dx can be compared simultaneously, or sequentially when new CA-ARTI-Dx guided assessment strategies are added to the trial. New tests will be eligible to add into the trial in the second winter and there will be an opportunity for SMEs and other companies to have their products evaluated in a rigorous clinical trial in the setting where the test is likely to be of greatest value.

Response adaptive platform trial

Co-primary outcome

The **first** co-primary outcome will be the **proportion of participants not prescribed any antibiotic** (of any dose or duration) at the initial consultation and over the subsequent four weeks.

The **second** co-primary outcome will be the **duration of severe symptoms** (symptoms rated as a 'moderately bad problem' or worse by patients) following the initial presentation.

Secondary outcomes

Secondary outcomes are:

- (i) Antibiotics (choice of antibiotic class, including dose, duration, whether 'delayed' or for immediate consumption) prescribed initially and dose and duration of overall antibiotic consumption during 4 weeks after inclusion, complication rates.
- (ii) Patient reported symptom severity, significant deterioration of illness (re-consultations, hospitalization, pneumonia, medication use, antibiotic use) and reported side-effects.
- (iii) Selection of pathogens with a resistant phenotype post therapy.
- (iv) Emergence of antibiotic resistance among the "normal" flora after therapy (part of Sub-study).

Clinical Sub-study

In addition, participants (approximately 200 individuals, depending on the number of CA-ARTI-DX we evaluate) will be invited to contribute to a sub-study where they will be more intensively characterised, investigated and followed up.

They will also contribute data to the main trial, but this sub-study will focus of the **selection of resistant pathogens and emergence of antibiotic resistance among normal respiratory and intestinal flora** after therapy, as well as for better characterization of known **immunological markers**.

Additional sampling for this sub-study comprises:

- Whole blood in PAX tubes at baseline and 2 days after enrolment
- Nasopharyngeal swab (in UTM or Amies) at 28 days
- Pharyngeal swab (in E-swab/Amies) at 28 days
- Stool samples at baseline and after 28 days

Psychological, social and organisational factors & process evaluation

A **mixed method process evaluation** will be carried out alongside the APT to capture data to explain how clinicians and patients adopt algorithms within outpatient practice for CA-ARTI consultations. We will select **4-5 countries** from the 10 that participate in the trial to be used as case studies that reflect the diversity of relevant factors such as care system, setting and use of antibiotics.

We will **build a theoretical framework** describing the mechanisms required for successful implementation.

Interviews **will capture perceived barriers and facilitators** to adoption of clinical algorithms and sustained use in daily clinical practice, and identify any additions and improvements required when rolling out diagnostics and support materials during the trial in order to meet clinicians' and patients' needs and enable use.

Health professionals (approximately 12 per country) will be purposively sampled to obtain variation in professional role, practice setting, and experience. **Patients** presenting with ARTI (approximately 12 per country) will be purposively sampled to obtain variation in age, use of diagnostic test in consultation and whether an antibiotic is prescribed. **Semi-structured topic guides** will be informed by existing literature and theory, including the Theoretical Domains Framework, to ensure that questions elicit likely key determinants of behaviour, and **Normalization Process Theory** to identify how clinical algorithms could be embedded in routine practice, and analysed using thematic and Framework analysis.

10 | 09 | 2019

Surbhi **Malhotra-Kumar** Carine **Malcus**

WP2

Laboratory Analyses & Biobank



Objectives

1. To identify the **aetiology of CA-ARTI** in a subset of participants in the WP4 trial, and to perform laboratory **validations of the pathogen and host-based CA-ARTI-Dx** evaluated in WP4, using samples obtained in the trial.
2. To **provide comprehensive data on the laboratory-based validations** (detection of pathogen, host biomarker, and AMR) of the CA-ARTI-Dx being evaluated on a regular basis in order to ‘machine-learn’ the clinical algorithms developed in WP1.
3. To **screen for host biomarkers** in an initial subset of blood/serum samples collected in WP4, and then validate these on the subsequent blood/serum samples from WP4.
4. To understand and **quantify the burden of AMR**, in a subset of nasal, pharyngeal and gastrointestinal samples, with respect to the type, days and doses of antibiotics prescribed based on the following outcomes: i) development or amplification of the AMR burden in the “normal” respiratory and intestinal flora after completion of antibiotic therapy, and ii) selection of pathogens with a resistant phenotype post therapy. These data will allow estimation of the cost of AMR and will feed into WP5.
5. To develop and support a **biobank** of well-characterized samples (including blood/serum and other relevant samples to be defined) and bacterial strains isolated from CA-ARTI patients.

Tasks

Task 2.1. Microbiology and biomarker research

(**UA**; BIOASTER, bMx, Accelerate)

2.1.1. Elucidating the aetiology of CA-ARTI and validation of pathogen and host biomarker based diagnostic interventions utilizing a machine-learning approach.

2.1.2. Evaluating host status and response (immune profile and biochemical markers) for host biomarker based diagnostic interventions and screenings.

2.1.3. Quantifying antimicrobial resistance and the associated microbiome in CA-ARTI patients.

Task 2.2. Create and maintain a biobank of clinical samples, pathogens and DNA isolated from CA-ARTI patients

(**IBBL**; UA, BIOASTER, ZON, FIND, UZA Third Party, bMx)

Task 2.1 Microbiology and biomarker research

2.1.1. Elucidating the aetiology of CA-ARTI and validation of pathogen AMR based diagnostic interventions utilizing a machine-learning approach.

Viruses, bacteria and AMR genes will be identified in relevant respiratory samples (sputum, nasopharyngeal samples, endotracheal aspirates, or pharyngeal samples based on the CA-ARTI-Dx requirements) from patients with symptomatic CA-ARTI utilizing a CA-ARTI-Dx and/or algorithm at the point of patient care in WP4.

Where respiratory samples are taken according to trial randomisation for the CA-ARTI-Dx, leftover portions of samples will be shipped to the central laboratory at Partner 1 UA for validation of test accuracy and other purposes. Furthermore, a battery of laboratory-based diagnostic tests, tailored for the viruses, bacteria, and AMR genes detected by the CA-ARTI-Dx test/algorithm in WP4, along with the appropriate respiratory samples, will be utilized as comparators.

Task 2.1 Microbiology and biomarker research

2.1.2. Evaluating host status and response (immune profile and biochemical markers) for host biomarker based diagnostic interventions and screenings

Baseline blood/serum samples collected from the same patients as in 2.1.1 will be utilized for host biomarker validations of trial-randomized CA-ARTI-Dx. Accordingly, this sub-task will validate (human) host biomarkers of infection included in the CA-ARTI-Dx being tested in WP4, and also develop an immune profile that will serve to distinguish infection from non-infectious causes, differentiate different aetiologies such as viral infection from bacterial causes, and for prognosis prediction.

As part of a sub-study, blood samples collected at baseline and after 2 days, in approximately 200 patients, will be investigated for biomarker evolution such as clearance of PCT and CRP as well for viral-induced proteins TRAIL and IP-10 that have been shown to identify viral aetiologies. In addition, several inflammatory mediators such as interleukin (IL)-1 β , IL-6, tumour necrosis factor (TNF)- α , and IL-8, shown to be differentially elevated in response to bacterial or viral infection, will be investigated.

These results will be fed in WP1 for the development of an optimal clinical algorithm.

Task 2.1 Microbiology and biomarker research

2.1.3. Quantifying antimicrobial resistance and the associated microbiome in CA-ARTI patients.

This task will utilize **WP4 sub-study samples**, both respiratory and stool, collected at the time of the primary consultation and before the start of antibiotic, respectively, and then at day 28, to qualitatively and quantitatively assess the AMR burden and changes therein as a function of the antibiotics used in the CA-ARTI patients.

Methods used: **quantitative culture** and **shotgun metagenomics** for identification and quantification of the bacterial aetiologies; shotgun metagenomics to distinguish bacterial and viral (co)aetiologies and identify viral pathogens; **whole genome sequencing** of *S. pneumoniae* and Gram negative pathogens by different technologies or hybrid assemblies (Illumina MiSeq short read sequencing or PacBio long read sequencing), for rapid prediction of MLST (Multilocus Sequence Typing) and antimicrobial resistance; For annotation, we will use Kraken, an automated metagenomics pipeline Metapipe v1, developed at UA, and Metaseq (bMx).

Task 2.2 Create and maintain a biobank of clinical samples, pathogens and DNA isolated from CA-ARTI patients

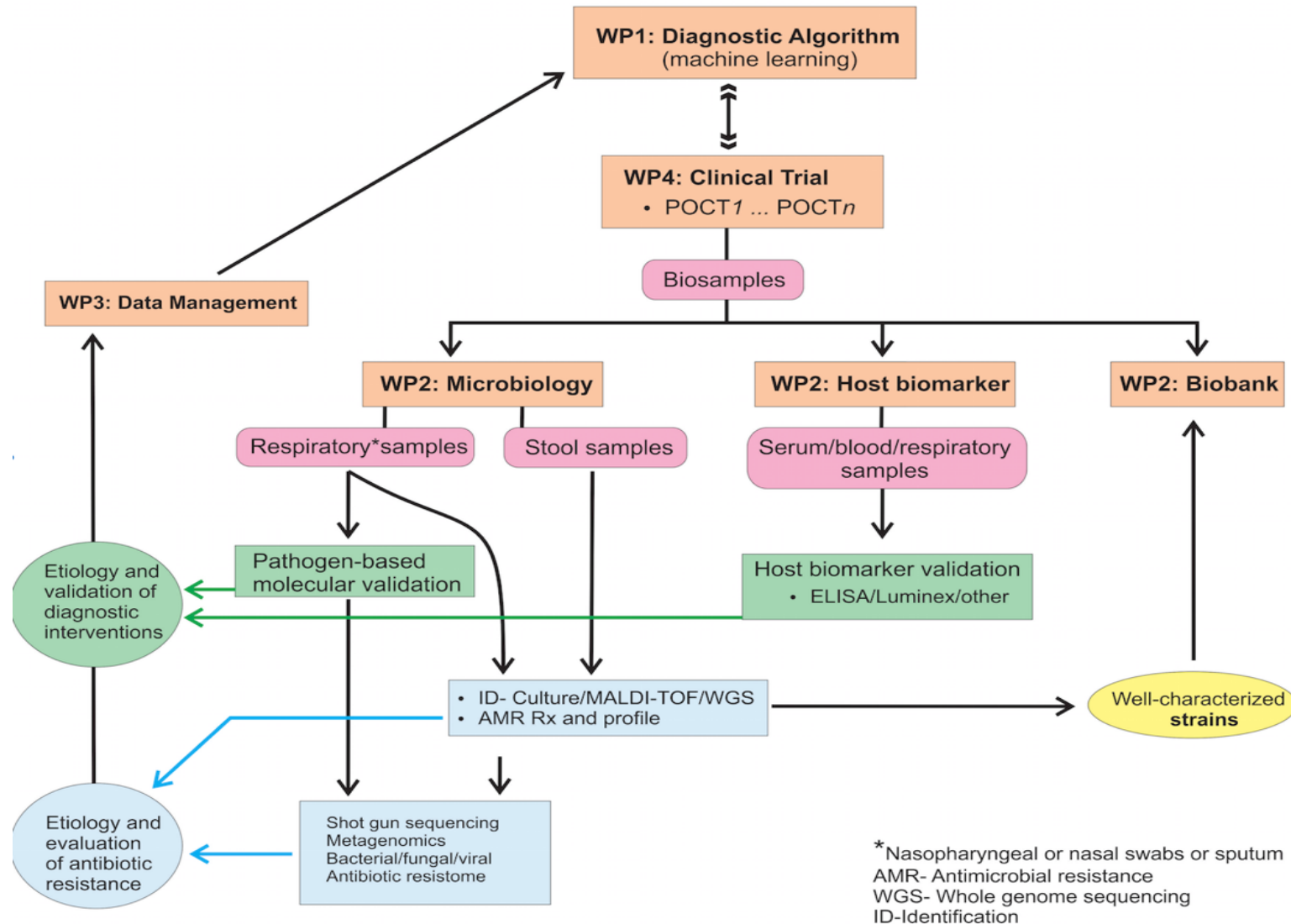
Samples (dedicated and leftover tubes) and strains will be stored at the UA-UZA biobank. Samples and DNA extracts remaining after laboratory analysis as well as cultured potential pathogens and antibiotic resistant commensals will also be added to the biobank.

Therefore, the VALUE-Dx Biobank will constitute a comprehensive collection of micro-organisms and clinical samples with high quality standards (redundancy, traceability, storage), obtained from the WP4 study.

The associated database will be developed with WP3, allowing data interoperability, and conform to the General Data Protection Regulation EU 2016/679.

In WP7, a business model will be developed to ensure its sustainability beyond the project funding period.

Sample flow & work up



Category	Characteristic	Content
General Information	Test	Name of the test
	Manufacturer	Name of the company that manufactures the product, not the selling company
	Intended use	What is the purpose of using the test?
	Setting	Location where the test will be performed (e.g. diagnostic lab, primary care, long-term care facilities, ICU, ED)
	Suitable for POC testing	Is the test suitable to be performed as Point of Care testing?
	Performer	Professional who will perform the test
	Patient type	Symptoms/characteristics of the patient for which the test should be applied
	Method	Method on which the test is based
	Targets	Molecule or molecules targeted by the method (i.e., antigen, specific gene,...)
	Analysis	Qualitative/quantitative/semi-quantitative
	Detection	Method by which the result is generated
	Detected pathogen	Organisms that the test can detect
	Detected AMR	Antimicrobial resistances directly detected by the test, both genotypic and phenotypic

Category	Characteristic	Content
Specifications	Storage conditions	Conditions of storage of the kit (i.e., temperature, humidity)
	Shelf life	Maximum storage time
	Kit components	What is included in the kit?
	Specimen	Type of sample for which the test is used
	Volume/amount required	Volume of sample required to start the test
	Test preparation	Steps to carry out before beginning to work with the sample
	Sample processing	Brief description of the steps that are needed to perform on the sample
	Controls	Internal test controls (i.e., controls that confirm the test is yielding a correct result)
	Calibration	Calibration requirements (i.e., frequency, material used...)
	Maintenance	Maintenance required for the instrument
	Hands on time	Estimated time that a trained performer has to be directly working (incubation times and analysis not included)
	Result readout	How the result is presented to the user
	Time to result	Estimated time required since the start of sample processing to result obtention (i.e., hands on time + instrument running)
	Instrumentation	Instruments required for test (i.e., detector, thermocycler)

Category	Characteristic	Content
Specifications	Instrument specifications	Specifications of the required instrument (i.e., size, weight, warm up time, etc.)
	Connectivity	Possibility to connect the care devices remotely and transfer test data to a central hub/lab
	Waste disposal	Way to dispose of the materials used (i.e., additional requirements apart from standard guidelines)
	Samples per run	Number of samples that can be tested in one run (i.e., single or multiple testing)

Category	Characteristic	Content
Validation	Patient population	Characteristics and number of the population in which the test has been validated. Please provide a dedicated table when possible
	Sensitivity	Analytic sensitivity of the test described by the manufacturer
	Specificity	Analytic specificity of the test described by the manufacturer
	PPV	Positive Predictive Value derived from the validation study
	NPV	Negative Predictive Value derived from the validation study
	Reproducibility	% of agreement between independent sites tested by the manufacturer
	Limit of detection	Minimal concentration of the organism/target required for the test to detect it
	Cross-reactivity	Organisms that can interfere in the result
	Interference	Compounds or sample characteristics that can interfere in the result

Category	Characteristic	Content
Company Capacity	Training required	Is training required for the user to perform the test?
	On-site training	Does the company offer the possibility to train the users?
	Cost of kit (€)	
	Instrument availability in Europe	Can the instrument be purchased in Europe and how many instruments can be made available per site?
	Cost of instrument (€)/leasing possibility	
	Calibration	Service offered by the company in order to set up the instrument in the setting
	Maintenance/Support	Support offered by the company to maintain the instrument
	Stage of development	Complete, in development, prototype
	Market region	Areas where the test can be purchased

Category	Characteristic	Content
Regulation	Regulatory approval	CE marked, FDA clearance
	CLIA complexity	Waived, moderate, high

Characteristic	Content
Clinical studies	List of references in which the test has been used (clinical studies, posters, etc.)
Website	

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Frank **Leus** Jean-François **Gorse**

WP3

Data Management & Analytics



Objectives

The overall objective of WP3 is to develop and implement the data management architecture capable for the storage, curation and reporting of the data generated within the project.

This is further divided into the following WP objectives:

1. To develop the **Data Management Plan** which will serve as the basis for all data management related activities in VALUE-Dx.
2. To develop and implement **the Point Prevalence Audit Study (PPAS) data collection tool** for WP4.
3. To develop and implement **data management systems for the response adaptive platform trial** of WP4.
4. To perform **full data management** of the response adaptive platform trial of WP4 in order to obtain a complete, correct and consistent database for analyses purposes.
5. To create and maintain the **central repository and user portal** comprising of all data collected in VALUE-Dx.
6. To assess and establish a **proof-of-concept data interoperability network** to allow connections between laboratory information systems and VALUE-Dx partners.

Tasks

Task 3.1 Development of Data Management Plan

(UMCU, FIND; bMx)

Task 3.2 Development of the web-based PPAS tool

(UMCU; bMx)

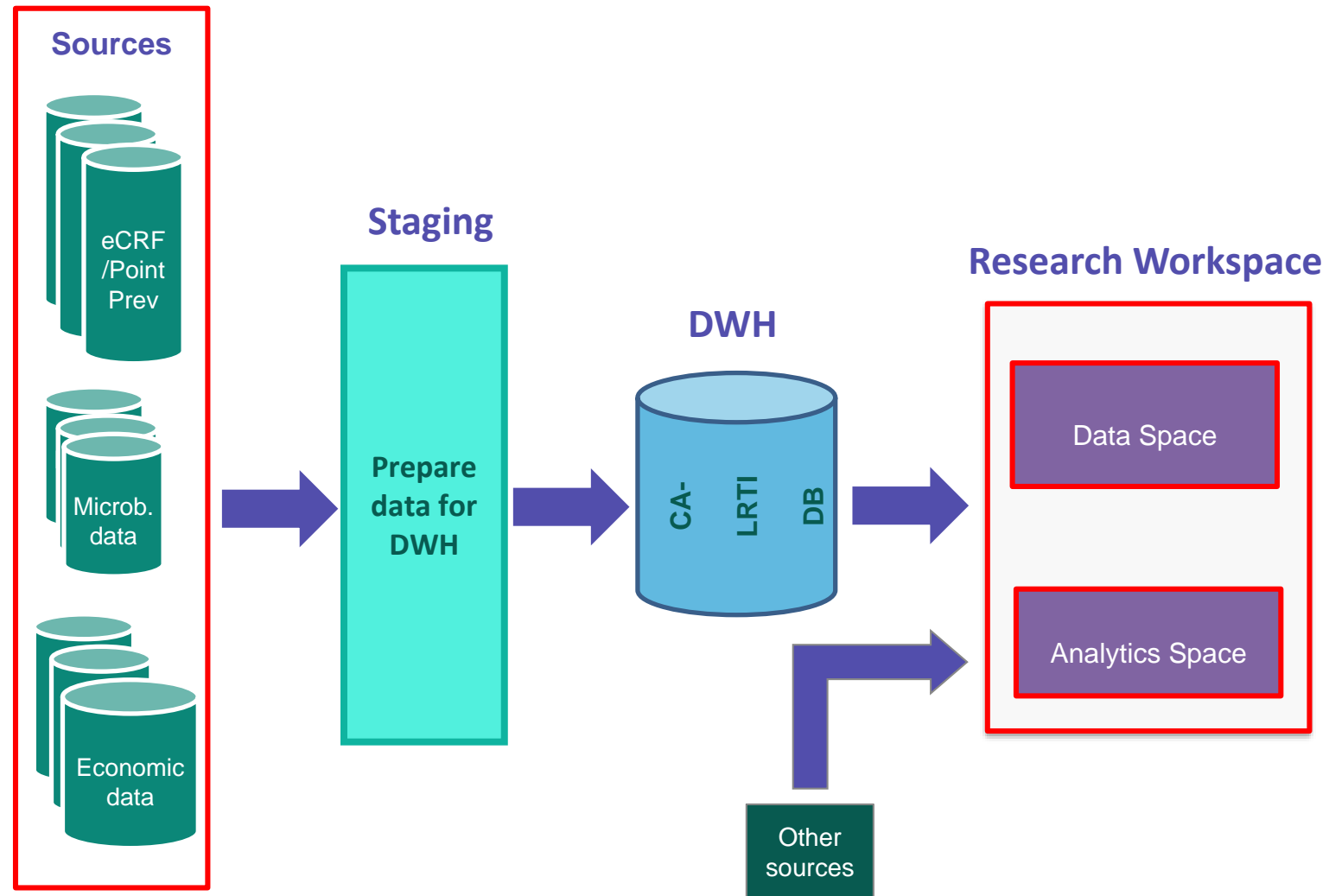
Task 3.3 Establish a database and repository of all data collected within VALUE-Dx

(UMCU; UA, IBBL, ZON)

Task 3.4 Assessment and establishment of a data interoperability network to allow connections between laboratory information systems and partners

(UMCU, FIND; ESCMID, bMx, Accelerate)

Data Management & Analytics



Task 3.4 Assessment and establishment of a data interoperability network to allow connections between laboratory information systems and partners

Phase 1 - Analysis

The approach will be to conduct an **initial investigation** to understand the availability and structure of existing data sets, platforms and diagnostics involved in COMBACTE LAB-Net (the laboratory network within COMBACTE-NET), and networks connected under the GA4GH vision, along with an inventory of other electronic systems (e.g. LIS and Middleware). The analysis will provide a Landscape Report and a Reference Architecture Report documenting.

Phase 2 - Proof of Concept (POC) system

This phase will identify and where practical, **deliver and operate a focused POC system**. The aim is to deliver a POC via configuration of existing available software and utilising standards-based interoperability (i.e. HL7, LOINC, SNOMED CT). The POC is expected to show a working example of how bacterial identification and Antibiotic Susceptibility Test (AST) data collection (as defined and implemented in task 3.3) can be automated. A selected number of labs will be connected.

Phase 3 – POC Report

This phase will produce a 'POC report' which will include a **case for implementation** of automation across all participating labs.

10 | 09 | 2019

Maarten **Postma**

Isabelle **Tongio**

WP5

Economic value, policies and innovative funding models



Objectives

1. Establish a **WP5 External Advisory Panel (EAP)** comprised of key stakeholders who are world-leaders on regulatory-HTA-payer systems, supplemented by internationally leading clinical experts in the use of diagnostics to fight AMR, able to provide the consortium with the necessary insights to ensure that VALUE-Dx activities and outputs are meaningful for regulators, HTA bodies, payers and clinical practitioners;
2. Develop **new health-economic models** to determine the long-term clinical, public health and economic impact of diagnostics in terms of AMR prevention with the support of HTAs reflecting the integral value of diagnostics;
3. To **support clinical trial development from the economic perspective** and perform an economic analysis on the WP4 clinical trial results;
4. Review and analyse the **current policy environment in Europe** and identify good practices for assessments of innovative diagnostics;
5. To develop **innovative frameworks to optimise assessment of the clinical and economic value of diagnostics** and facilitate sustainable funding systems over the entire lifetime of the diagnostic;
6. Develop and apply a proposal for a mechanism to ensure **transferability of findings** into other countries' settings;
7. Develop proposals for **fit-for-purpose policies**, to accelerate market entry of and accessibility to cost-effective diagnostics with the potential to be applied to cost effectively reduce AMR.
8. Explore and define the **organisational, structural, ethical and social factors influencing widespread adoption of CA-ARTI-Dx** by community care organisations across European countries and develop recommendations to facilitate implementation of diagnostics in routine clinical practice.

Tasks

Task 5.1 Establishment, maintenance and management of a WP5 regulatory-HTA-payer EAP

(**NICE**; GÖG, UMCG, bMx)

Task 5.2: Review of the current HTA environment and methodologies, inclusive health-economic frameworks, and models, used for valuing diagnostics and analysing antibiotic resistance

(**UNIRIOJA, UMCG**; NICE, GÖG, bMx)

Task 5.3 Trial-based health-economic analysis of (rapid, localised) diagnostics strategies in close collaboration with WP4

(**UNIRIOJA**; UA, NICE, bMx)

Task 5.4 Development of a health-economic model for cost-effectiveness of diagnostics beyond the trial-based setting

(**UMCG**; OECD, NICE, UA, UMCU, bMx, BD, Accelerate, Janssen)

Task 5.5 Analysis of existing and potential innovative policies applied to include new diagnostics in the care systems of European countries with a view of identifying good practice and a proposal for enhancing fit-for-purpose policy frameworks related to HTA, pricing and funding mechanisms

(**GÖG**; NICE, UMCG, UNIRIOJA, bMx)

Task 5.6 Transferability of health-economic approaches and results of such transfers between countries, notably to H2020 Associated Countries

(**OECD**; UNIRIOJA, BU, bMx)

Task 5.7 Interviewing stakeholders on policy and regulatory factors

(**UOXF, UA**; UNIRIOJA, GÖG)

Composition of the VALUE-Dx External Advisory Panel (EAP)



Task 5.1 Establishment, maintenance and management of a WP5 regulatory-HTA payer EAP

Roles:

- To engage actively in discussions and provide feedback (serve as sounding board) and input into topics brought forth in VALUE-Dx on research activities, case studies and outputs;
- To contribute to the design of an innovative fit-for-purpose HTA system of the clinical- and economic value of diagnostics to support more targeted prescription and use of antibiotics and reduce AMR.

Composition:

Consisting of 10-15 individuals.

Role of the industry:

The WP5 EAP will be independent from industry. However, industry will be involved in two ways:

- Helping to establish the WP5 EAP by suggesting members of European regulatory-HTA-payer organizations to invite;
- Securing interactions between industry and the WP5 EAP (via the industry partners in VALUE-Dx, and via Medtech Europe and BEAM Alliance serving on the overall VALUE-Dx EAP).

Task 5.2: Review of the current HTA environment and methodologies, inclusive health-economic frameworks, and models, used for valuing diagnostics and analysing antibiotic resistance

1. **Review** HTA frameworks that have been applied for analysing diagnostic strategies in antibiotics use. These frameworks will include both health-economic models that focus only on the short-term impact of diagnostic strategies, as well as models incorporating AMR and longer-term and broader economic impacts for society.
2. **Selection** of some approaches rendering a generic modelling framework to be applied for various diagnostic strategies and countries and to be further developed in the project (tasks 5.3 and 5.4). Selection criteria: transparency, applicability and quality of the approaches proposed, baseline epidemiological parameters (in close co-operation with WP1).
3. **Continuously updating** during the project: expected changes of the HTA-environment in the European countries; annual literature reviews.

Task 5.3 Trial-based health-economic analysis of (rapid, localised) diagnostics strategies in close collaboration with WP4

Health-economic analysis of the **WP4 clinical trial** using traditional health-economic methods (to be extended in task 5.4), specific for the adaptive platform design, both on primary and secondary endpoints. Economically relevant parameters will also be collected within the preceding **WP4 Point-Prevalence Audit Study** (PPAS).

Approaches:

- Decision-tree approach with state-of-the-art methods, including the appropriate specification of base case, sensitivity, threshold and scenario analyses, positive and negative predictive values of the CA-ARTI-Dx
- Stochastic analytic approaches, including sensitivity and value-of-information analyses.

Outcomes of the model:

Primary outcome: reduced use of antibiotics in relation to costs of tests and predicted health-care savings.
Other outcomes: feasibility of estimating and usability of the Quality-Adjusted Life Years (QALYs).

Task 5.4 Development of a health-economic model for cost-effectiveness of diagnostics beyond the trial-based setting

Second health-economic model to investigate the long-term effects of the implementation of CA-ARTI-Dx (i.e., beyond the clinical trial's time frame).

Information on costs and cost-effectiveness will be evaluated using methods such as the current ISPOR guidance for Good Practice in Decision Analytic Modelling and Value Assessment in Care.

Will enable prioritization of specific CA-ARTI-Dx using resource and costs data on the one hand and the clinical and health outcomes on the other hand.

Outcome of the model:

Primary outcome: Incremental Cost-Effectiveness Ratio (ICER) where health outcomes are measured in quality-adjusted life-years (QALYs).

Other outcomes: cost of implementation, net monetary benefit, cost per infection correctly identified, and cost per complication averted.

Countries modelled:

Selection among those countries involved in the clinical trial as well as other EU Member States and H2020-associated countries, depending on data availability and reflecting a variety of Health systems, AMR profiles and geographies.

Task 5.5 Analysis of existing and potential innovative policies applied to include new diagnostics in the care systems of European countries with a view of identifying good practice and a proposal for enhancing fit-for-purpose policy frameworks related to HTA, pricing and funding mechanisms

Aim:

To map policies related to market launch, pricing and funding of diagnostics for CA-ARTI in the EU Member States and a few H2020 Associated countries and to identify good and less successful practices to implementation of HTA and adoption of diagnostics in this field.

Aspects:

Policies and approaches of authorities/agencies (national and regional HTA bodies, payers, ...) in assessing the value of these diagnostics, determining the price, managing the entry and applying funding models of CA-ARTI Dx in the community setting. The survey will be done according to the predefined framework of meta-indicators to allow for comparability between countries, as far as possible.

Countries analysed:

At least 15 EU Member States/H2020 Associated countries.

Task 5.5 Analysis of existing and potential innovative policies applied to include new diagnostics in the care systems of European countries with a view of identifying good practice and a proposal for enhancing fit-for-purpose policy frameworks related to HTA, pricing and funding mechanisms

Method:

First step: literature research that considers both peer-reviewed and grey literature (in national languages) to populate the country brief. Second step: collect information through a detailed questionnaire-based survey with competent authorities in surveyed countries. Information collected in this mapping exercise will feed the qualitative interviews done in task 5.7, the WP5 EAP in task 5.1.

Outcome:

- A draft set of recommendations of how to improve existing pricing and funding policies to ensure timely accessibility of cost-effective diagnostics able to reduce AMR.
- Final recommendations with fit-for-purpose framework based on Delphi process with the WP5 EAP.

Task 5.6 Transferability of health-economic approaches and results of such transfers between countries, notably to H2020 Associated Countries

Aim:

To address the issue of heterogeneity that exists between countries – in terms of infectious agents' incidence, resistance rates, health-care system characteristics and price levels – by providing estimates of health-economic impact that directly relevant to individual countries. .

To identify and shortlist the most influential parameters for their relevance in transferring models and results.

Outcome:

Minimal datasets that can be applied in countries with limited data availability as opposed to optimal datasets for countries with rich data availability.

Data sources:

Epidemiological data: European Centre for Disease Prevention and Control, individual countries, international registries and databases (such as the WHO Global Antimicrobial Resistance Surveillance System or the Centre for disease Dynamics, Economics & Policy); Demographic data: institutional sources such as Eurostat database and the United Nations' World Population Prospects database

Task 5.7 Interviewing stakeholders on policy and regulatory factors

Setting:

- Interview stakeholders across 6-8 EU Member States and potentially H2020-associated countries. Selected based on variation in health service delivery and are likely to overlap with countries involved in the trial in WP4.
- Approximately 6 participants per country, giving a total of around 40 interviews.

Purpose:

- To seek to understand the interests and influence of individuals or groups, and to assess the readiness of key stakeholders, in adopting diagnostics in community care settings.
- To help to identify policies and regulations which influence the use of diagnostics in community care settings in these countries.

Method:

- Interview will follow a semi-structured topic guide, informed by the literature review and survey carried out in tasks 5.2 and 5.5.
- Data will be analysed using thematic and framework analysis to identify common themes both within and between countries.

Task 5.7 Interviewing stakeholders on policy and regulatory factors

Outcome:

Analysis of the barriers and facilitators to the adoption of diagnostics, from the perspective of policy makers, in each of the countries studied and will identify similarities and key differences between countries.

Propose either universal approach to adoption of diagnostics or whether tailored strategies need to be incorporated for adoption in certain contexts.

As a whole, interviews from WP4 and WP5 will provide detailed data on the perspectives of patients, professionals and policy makers taking a socio-ecological approach. The Socio Ecological Model (SEM) will help identifying barriers and facilitators to the adoption of diagnostics within individuals (micro system), organisations (meso systems) and policy (macro systems).

These qualitative data will be fed into task 6.4 to ensure that the development of e-learning modules is tailored appropriately to the needs of the target group.

10 | 09 | 2019

Murat **Akova**

Renuka **Gadde**

WP6

Education & Advocacy



Objectives

1. To disseminate the findings generated in VALUE-Dx by using various forms of communication and educational activities and publications at all levels of stakeholder platforms to promote their uptake and implementation in daily clinical practice and policy;
2. To develop innovative, effective ways to disseminate information for creating awareness of optimal diagnosis and prognosis of CA-ARTI to prevent unnecessary prescription and use of antibiotics, to improve coverage with antibiotics, and thus limit antibiotic resistance and associated health and socioeconomic impacts;
3. To develop and to tailor materials to support the adoption of CA-ARTI-Dx in European community care settings.
4. To develop and implement the VALUE-Dx Course.

Tasks

Task 6.1. Dissemination of information

(**ESCMID**; ERS, UOXF, UA, BD, Accelerate, Janssen)

Task 6.2. Publications

(**ESCMID, ERS**; Janssen)

Task 6.3 Developing materials and modules to support adoption of diagnostics

(**ERS**; ESCMID, UOXF, UA, bMx, BD, Accelerate, Janssen)

Task 6.4 Developing and implementing the VALUE-Dx Course

(**UA** in collaboration with all other WPs as represented by the WP Co-leads)

Task 6.1 Dissemination of information

For professional healthcare organisations:

- Annual international conference of ESCMID and ERS (e.g. post-graduate course, meet the experts, symposium);
- Webinars organized jointly by ERS and ESCMID during the entire project;
- Collaboration with other relevant international organisations to organise symposia.

For consumer organisations and general public:

- Social media tools including short informative videos (YouTube, Facebook and similar social media platforms) will be designed in collaboration with consumer organizations;
- Media information campaigns;
- Designing smartphone and computer applications for both primary care physicians and specialists;

For policy makers:

- Policy recommendations and white papers;
- Participation to European health policy and health economy events (e.g. World Health Summit, European Health Forum, ISPOR Europe, IMI stakeholder meetings)

Task 6.2 Publications

Quarterly newsletter, consensus report and a white paper on 'the role of rapid diagnostics for antimicrobial stewardship in CA-ARTI' will be produced by joint efforts from ESCMID and ERS.

Communicated and distributed by both Societies to their membership and to the affiliated societies eventually reaching >60.000 scientists and practicing physicians throughout the world, and their annual meetings.

Joint guideline update on 'the management of adult respiratory tract infections' which was originally published in 2011 by ESCMID and ERS.

Lay public information document in collaboration with consumer organizations;

Communicated both in print and online for the lay public particularly targeting school children and their parents.

Task 6.3 Developing materials and modules to support adoption of diagnostics

E-learning modules:

Mobile learning Apps; case studies based on slides or short videos'; live webinar; short modules topic oriented.

ePortal (through the ERS e-learning platform):

- Document Library for storage of PowerPoint slides, documents, images, handouts, media files, live streamed webinars.
- Connected to a Learning Management System (Moodle): processing of CME/MOC/CE certified learning modules and certificates.
- Available on iOS and Android apps for both mobile phones and tablets.

Task 6.4 Developing and implementing the VALUE-Dx Course

First course:

- Internal
- At kick-off

Second course:

- Internal
- First Annual meeting

Third course:

- Open to external parties
- Final year four

Beyond VALUE-Dx project:

- A self-supporting (annual) course

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Herman **Goossens**

Philippe **Cleuziat**

Tim **Jinks**

WP7

Project Management & Sustainability



VALUE-Dx overall organisational design

Public-private partnership between:

- EFPIA partners (BioMérieux, Janssen Diagnostics and Abbott);
- IMI-JU2 Associated Partners (AP) (Accelerate Diagnostics, Bio-Rad, Becton Dickinson and the Wellcome Trust);
- Public sector (academia) organisations and SMEs.

Objectives

1. To ensure compliance with the **EC Grant Agreement and Consortium Agreement**, and to ensure that the projects agreed deliverables and milestones are achieved within budget, and on time;
2. To ensure the **effective inter-WP alignment** of activities and promote efficient and effective internal communication and decision-making;
3. To develop a feasible **business plan** for the sustainable continuation of the operational infrastructures and processes needed to continue the VALUE-Dx activities well beyond the projects 4-years, and to widen the applicability of study findings beyond the current priority of CA-ARTI in community care settings.

Tasks

Task 7.1 Project management

(UA, bMx, Wellcome)

Task 7.2 Establishment, maintenance and management of a multisectoral, External Advisory Panel (EAP)

(UA; bMx UNIVR, UEDIN, NICE, ESCMID)

Task 7.3 Development of an integrated business and sustainability model

(UA, bMx; UMCU, Strategy Consulting Firm (to be tendered))

7.3.1 Develop a business plan for creating and maintaining a biobank of clinical specimens, strains and DNA
(IBBL; ZON, FIND, BIOASTER, UA, bMx, UZA Third Party).

7.3.2 Develop a business plan for creating and maintaining an integrated database
(UMCU; bMx, UMCU, FIND)

Governance (1)

Coordination Team (CT):

- Consisting of the Project Coordinator/ Project Lead (Herman Goossens of P1 UA), Industry Lead (Phillippe Cleuziat of bMx) and the Wellcome Lead (Tim Jinks of Wellcome)
- Meets every two weeks by TC (+ Project manager, David De Pooter)

Executive Board (EB):

- Consisting of WP Co-Leads + Project manager (non-voting member)
- Central management unit, responsible for coordinating the activities at project level
- Monitors the progress (technical and financial) of the activities against milestones and will report to the GA and – on behalf of the GA – to IMI-JU
- Assesses the overall scientific quality of the results, the overall project-performance of the partners and potential risks that may delays or significantly impact on the project and will propose corrective actions to the GA for decision-making, if and when necessary
- Meets every month by TC and every 6 months F2F
- Chair: Project Leader

General Assembly (GA):

- Consisting of all VALUE-Dx partners: each partner has one vote + Project manager (non-voting)
- Decision-making body for all major consortium and/or project level issues, such as the consortium composition and Grant Agreement
- Meets annually F2F
- Chair: Project Leader

Governance (2)

Project Support Office (PSO):

- Consisting of the Project Manager (PM), Pieter Moons of P1 UA, a central Financial Administrator, and secretarial-organisational support staff
- Based at University of Antwerp
- Role: to support the EB/EBLT and GA in the execution of their tasks

WP Co-Leads:

- Each WP will be led by a team of two WP co-leaders: one from EFPIA/PA and one from the academic partners
- Role: responsible for coordinating the activities in their WP, monitoring the progress towards the WP milestones and deliverables, ensuring efficient and agreed budget utilization, and reporting the progress to the EB
- They will have the authority to take decisions within their WPs that do not affect other WPs (e.g. minor shift in budgets and tasks)
- Each WP is organized into several tasks with a designated task leader

Governance (3)

Community Care Research Organisations (CCROs) and National Facilitators:

- Within WP4, National Facilitators will be appointed for each CCRO by country
- The UOXF Primary care and Vaccines Clinical Trials Unit will take overall management of regulatory aspects, and the UMCU's Julius Centre will cover study set up, training, initiation and logistics

Stakeholder Advisory Boards (SAB):

- Role: strategic sounding board for the WPs
- A substantial budget of **€576.000** has been set aside in the budget of Partner 1 UA to reimburse the EAP members for travel and subsistence costs incurred

INTERVIEWEES [1/3]

- Aim: 20 interviews max., covering **broad spectrum of interviewees that can bring different insights**
- Currently 27 interviewees selected, including:

INDUSTRY

Organisation	Interviewee name	Function	Type	Part of Value-Dx consortium?	Perspective
Abbott Diagnostics	Felicia Longobardi	EMEA Marketing Director (point of care)	Diagnostics	Yes	European
Becton Dickinson	Adam Zerda	Director, Antimicrobial Resistance Strategy and Program Development	Medical devices	Yes	Outside Europe
bioMérieux	Philippe Cleuziat	Innovation Program Senior Director; VALUE-Dx industry lead	Biotechnology	Yes	European
GlaxoSmithKline	David Payne	VP Infectious Diseases & Senior Site Leader Upper Providence (US R&D Hub)	Pharmaceutical	No	Global
Janssen Diagnostics	Jorge Villacian	Chief Medical Officer	Medical devices	Yes	Global
MedImmune (AstraZeneca)	Hasan Jafri	Clinical Lead, Serious Bacterial Infections; IMI; COMBACTE	Biotechnology	No	Outside Europe
Pfizer	Rienk Pypstra	VP GPD Anti Infectives; COMBACTE	Pharmaceutical	No	Global
Qiagen	Uwe Oelmueller	Vice President MDx Development EU Sample Technologies	Biotechnology	No	European
Roche Diagnostics	Michael Hombach	Director, Senior Global Clinical Leader Infectious Diseases, Centralised and Point of Care Solutions	Pharmaceutical	No	European
Thermo Fisher Diagnostics	Verena Murer-Waser	POC Specialist	Pharmaceutical	No	European

INTERVIEWEES [2/3]

NON-INDUSTRY

Organisation	Interviewee name	Function	Type	Part of Value-Dx consortium?	Perspective
BEAM Alliance	Marc Gitzinger	VP of the Board	Biotechnology	No	European
BBMRI-ERIC	Francesco Florindi	Strategy & Partnership Manager	Research	No	European
British In Vitro Diagnostics Association (BIVDA)	Doris-Ann Williams	Chief Executive	Hospital & healthcare	No	European
EORTC	Denis Lacombe	Director General	Clinical research	No	European
ESCMID	Evelina Tacconelli	Education Officer for Infectious Diseases and Clinical Microbiology	Hospital & healthcare	No	European
ESCMID	Jesús Rodríguez Baño	President	Hospital & healthcare	Yes	European
Foundation for Innovative New Diagnostics (FIND)	Stefano Ongarello	Head of Data Services and Biobanking	Research	Yes	European
Integrated BioBank of Luxembourg (IBBL)	Fay Betsou	Chief Biospecimen Science; Biobank database business plan task lead	Biobank	Yes	European
JPIAMR	Laura Marin	Head of Secretariat	AMR Research	No	European
London School of Hygiene and Tropical Medicine	Rosanna Peeling	Professor and Chair of Diagnostic Research	Public health	No	Global
Swiss Biobanking Platform	Sabine Bavamian	Governance Manager	Biobank	No	European
UK Biobank	Chris Boulton	Chief Information Officer	Biobank	No	European

INTERVIEWEES [3/3]

Organisation	Interviewee name	Function	Type	Part of Value-Dx consortium?	Perspective
UMC Utrecht	Marc Bonten	Professor; COMBACTE-Net coordinator	Hospital & healthcare	Yes	European
University of Antwerp (UA) and University Hospital (UZA)	Herman Goossens	Professor; PREPARE; ECRAID-Plan and VALUE-Dx project leader	Hospital & healthcare	Yes	European
University Hospital Antwerp	Manon Huizing	Director of biobank UA-UZA	Biobank	Yes	European
Wellcome Trust	Tim Jinks	Head of Drug Resistant Infections Program; VALUE-Dx Wellcome lead	Public health	Yes	European
WHO	Francis Moussy	Leader, Diagnostics & Other Health Technologies & Focal Point for New Ebola Diagnostics	Public health	No	Global

› *Regulatory bodies will be added later on*

INTERVIEW QUESTIONNAIRE [1/2]

- Objective of interviews is to **validate infectious diseases diagnostics market characteristics and gain insights into appetite & expectations regarding Value Dx's business plan development** (especially concerning potential services to be offered)
- Interviews of 1-2 hrs. face-to-face or by TC
- Selection of questions to be asked depending on background & experience of interviewee

A. General	
A. 01	What is your role in the (infectious diseases) diagnostics market space/ecosystem?
A. 02	What are your vision, mission and strategic priorities within this space?

B. Infectious diseases diagnostics market & trends	
B. 01	Looking at the infectious diseases diagnostics market: what are its characteristics?
B. 02	What is the size of the market?
B. 03	What are market drivers and barriers? How could we overcome potential barriers?
B. 04	Who are the key players in the market? Would you say the market is rather fragmented (i.e. many small players vs. few large players)?
B. 05	What are the innovations? Anything in particular that you observe when looking at company pipelines? Do you think there is an increasing/decreasing interest to develop new diagnostics for infectious diseases?
B. 06	What are characteristics of successful diagnostics?
B. 07	What differentiates a diagnostic device or platform with broad adoption/usage from one that has a more niche application?
B. 08	Where is most added value (e.g. regulation, clinical aspect, reimbursements) created today? Do you believe that this will change towards the future?

B. 09	For which indications are most new diagnostics created? Is there an unmet need? Infections without sufficient diagnostics? Why is that the case according to you?
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C. Development & commercialisation of new diagnostics	
C. 01	What would you consider as today's most important challenges (e.g. financing, market adoption, regulation) in the development of new diagnostics?
C. 02	What are the trends regarding the placement of diagnostics in other settings than today (e.g. pharmacy, supermarket, online via apps)? What is the (potential) impact of such trends on the value chain? How fast do you believe that we will see this phenomenon in Europe?
C. 03	What is the added value of the WHO pre-qualified list of diagnostics (<i>essential list of diagnostics vs. specific list on AMR</i>) relative to the CE-marking? Is there an impact on commercialisation?

D. Biobanks	
D. 01	How would you define a biobank? (e.g. infrastructure that provides service and holds collections vs. the collection itself)
D. 02	What are the challenges - if any - in finding samples of the necessary quantities and characteristics today? How do you deal with this?
D. 03	How should/can samples be shared? Who should have access? Under which conditions? What would it take for you to be willing to share 'your' samples?

INTERVIEW QUESTIONNAIRE [2/2]

D. 04	What types of interactions do you have with biobanks?
D. 05	Which services are already offered in the market to ease this process?
D. 06	Do you have any fixed contracts in place with specific biobanks?
D. 07	How would you describe the dynamic between different biobanks?
D. 08	<i>For the owners of databases & biobanks:</i> what are some of the challenges (e.g. funding, quality control, maintenance) that you face? How can these potentially be overcome?

E. Data

E. 01	What type of data (e.g. clinical, economical) do you collect? How do you deal with this data? Which data management systems do you use?
E. 02	Openness of data: what does this mean for you? Which data should be transparent vs. be kept confidential?
E. 03	Is there a need to have access to data collected by others? Why?
E. 04	How should/can data be shared? Who should have access? What are the most important hurdles for data sharing (e.g. privacy, data quality)? What would it take for you to be willing to share 'your' data?
E. 05	How can increased use of data improve or enhance the role of diagnostics in infectious disease management?
E. 06	What is important in the governance (e.g. capturing, management, sharing) of data? What power will different stakeholders (incl. patients) have here?

F. Regulation

F. 01	Which impact does regulation have on the development of new diagnostics? What is the regulatory process linked to the development of new diagnostics? Would you perceive it as a market barrier?
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F. 02	What are the challenges with regards to regulatory aspects? (Incl. ethical issues) How do you believe these might evolve towards the future?
F. 03	To which extent do the regulatory agencies take up an active/passive role?

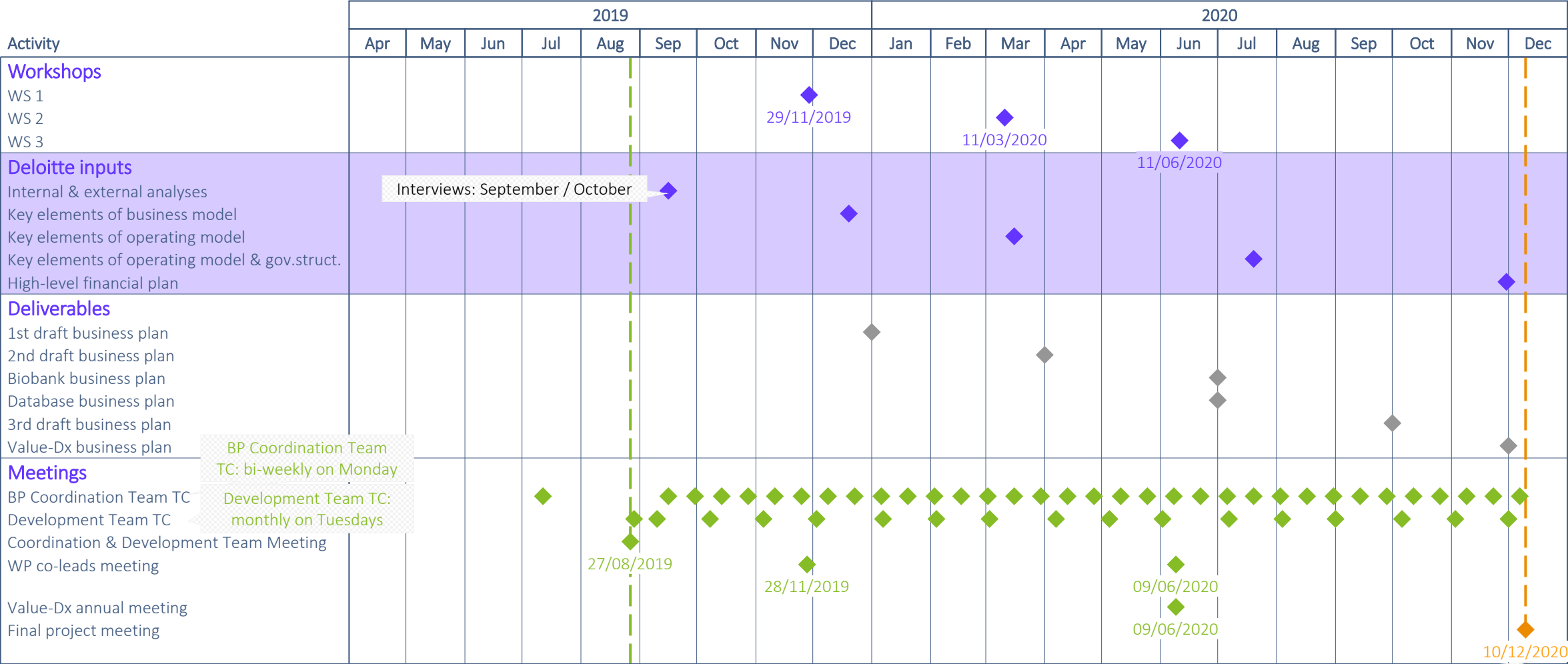
G. VALUE-Dx

G. 01	To which extent are you aware of the existence of the VALUE-Dx project?
G. 02	In your understanding, which market need(s) should VALUE-Dx aim to address/provide an answer to? How could VALUE-Dx help organisations active in the ecosystem to overcome the aforementioned barriers?
G. 03	What do you see as the (potential) role for VALUE-Dx in terms of services offering? (Role as a biobank or link between biobanks? Role in data management?) Are there 'no-go' areas?
G. 04	What should Value-Dx offer in order to have researchers use its services?
G. 05	Are there unmet needs or specific indications VALUE-Dx should focus on?
G. 06	What should its geographical scope be? Is Europe broad enough?
G. 07	With this scope in mind, how would you see your interaction and role linked to VALUE-Dx?
G. 08	What are important (operational) implications for Value-Dx in its set up?

H. Miscellaneous

H. 01	Are there any other items you would like to mention/stress that we did not discuss yet in the questions so far?
H. 02	Thinking about the scope of this project, are there any other people you would recommend us to interview?

PROJECT TIMELINE & STATUS UPDATE



◆ = Deloitte to take lead ◆ = Deloitte to join

- Work in progress -

Together with ECRAID: present coherent overall Business Plan



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