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UZ LEUVEN

The effect of evidence-based order sets within a CPOE (computerised physician order entry) system on the quantity and quality of laboratory test ordering in family practice: a cluster randomised trial

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GENERAL INFORMATION

TITLE PAGE

FULL TITLE OF THE TRIAL

The effect of evidence-based order sets within a CPOE (computerised physician order entry) system on the quantity and quality of laboratory test ordering in family practice: a cluster randomised trial

SHORT STUDY TITLE / ACRONYM

Evidence-based order sets for laboratory tests

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in " Directive 2001/20/EC",), and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:		
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TRIAL SUMMARY

Trial Title	The effect of evidence-based order sets within a CPOE (computerised physician order entry) system on the quantity and quality of laboratory test ordering in family practice: a cluster randomised trial.	
Short Title	Evidence-based order sets for laboratory test ordering	
Trial Reference	KCE 16011	
Trial Design	Cluster randomised controlled trial	
Trial Participants	Primary care physicians affiliated to one of three collaborating laboratories in the Leuven, Ghent or Antwerp regions	
Planned Sample Size	300 physicians randomised, data collected for 12 000 patients	
Intervention duration	3 months	
Follow up duration	6 – 12 months	
Planned Trial Period	3 years	
Objectives		Outcome Measures
Primary	To compare the effect of evidence-based order sets versus control on the proportion of appropriate laboratory tests ordered by primary care physicians	Proportion of appropriate tests per indication according to guidelines
Secondary	To compare the effect of evidence-based order sets versus control on diagnostic error by primary care physicians	Number of missed diagnoses at end of trial
	To compare the effect of evidence-based order sets versus control on the volume of laboratory tests ordered by primary care physicians	Number of ordered tests at end of trial
Exploratory	To evaluate the implementation process before the intervention	
	To evaluate the sustainability of the intervention	
	To evaluate the effect of the intervention on downstream activities	
	To evaluate physician satisfaction with the intervention	
Ethics committee	UZ Leuven	
Privacy commission	Sector Committee for Social Security and Health	

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
BELGIAN HEALTH CARE KNOWLEDGE CENTRE Administrative Centre Botanique (Doorbuilding) Boulevard du Jardin Botanique 55 B-1000 Brussels, Belgium	

ROLE OF STUDY SPONSOR AND FUNDER

UZ/KU LEUVEN as mentioned in KEY TRIAL CONTACTS shall act as sponsor of the Study, as defined in the Law of 2004, and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2004. **UZ/KU LEUVEN** shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with the Study Subjects or the Regulatory Authorities as sponsor of the Study. **UZ/KU LEUVEN** acknowledges and agrees for the avoidance of doubt that KCE shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and **UZ/KU LEUVEN** shall make no representations whatsoever in this respect.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Trial Management Committees

Trial Steering Committee

The Trial Steering Committee (TSC) consists of the following participants:

- **UZ Leuven Clinical Trial Center**
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- **Department of Family Medicine and Primary Health Care, Ghent University:** Prof Dr An De Sutter
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- **Flemish College of Family Physicians, Domus Medica:** Dr Hanne Cloetens

The TSC will be responsible for planning, conducting and reporting on the trial. This committee will convene on a quarterly basis, and more frequently when deemed necessary. The trial funder (KCE) has the right to be present at the TSC meeting. Meetings will be planned and reports sent to the trial funder (KCE).

Protocol contributors

The following participants contributed to the protocol.

Dr Nicolas Delvaux: responsible for setting up the study design, drafting the first draft of the protocol and integrating remarks on subsequent drafts.

Prof Dr Bert Aertgeerts: responsible for setting up the study design and commenting on each of the drafts of the protocol.

Prof Dr An De Sutter: responsible for commenting on each of the drafts of the protocol and amending the study design.

Prof Dr Dirk Ramaekers: responsible for commenting on each of the drafts of the protocol and amending the study design.

Prof Dr Steffen Fieuws: responsible for developing data analysis strategies and sample size calculations and commenting on each of the drafts of the protocol.

Ms Ann Belmans: responsible for developing data analysis strategies and sample size calculations and commenting on each of the drafts of the protocol.

Mr Stijn Van de Velde: responsible for setting up the study design and commenting on each of the drafts of the protocol.

Prof Dr Jeroen Luyten: responsible for detailing necessary variables for economic evaluation and commenting on each of the drafts of the protocol

KEY WORDS:	Evidence-based medicine, appropriate laboratory test ordering, order sets, primary care, implementation

LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

ABBREVIATION	DEFINITION
AML	Algemeen Medisch Laboratorium
APR	Annual Progress Reports
CCDSS	Computerised Clinical Decision Support System
CDSS	Clinical Decision Support System
CI	Chief Investigator
COMET	Core Outcome Measures in Effectiveness Trials
CPOE	Computerised Physician Order Entry
CRF	Case Report Form
CRT	Cluster Randomised Trial
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
EBM	Evidence-Based Medicine
EBV-IgG	Epstein-Barr Virus Antibodies
EHR	Electronic Health Record
GCP	Good Clinical Practice
GP	General Practitioner
GEE	Generalised Estimating Equations
HD4DP	Health Data for Data Provider
HD4RES	Health Data for Research
ICC	Intracluster Correlation Coefficient
ICF	Informed Consent Form
INR	International Normalised Ratio
ISF	Investigator Site File
KCE	Belgian Healthcare Knowledge Centre
LIS	Laboratory Information System
MCH	Medisch Centrum Huisartsen
PCP	Primary Care Practice
PI	Principal Investigator
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
WIV-ISP	Scientific Institute For Public Health

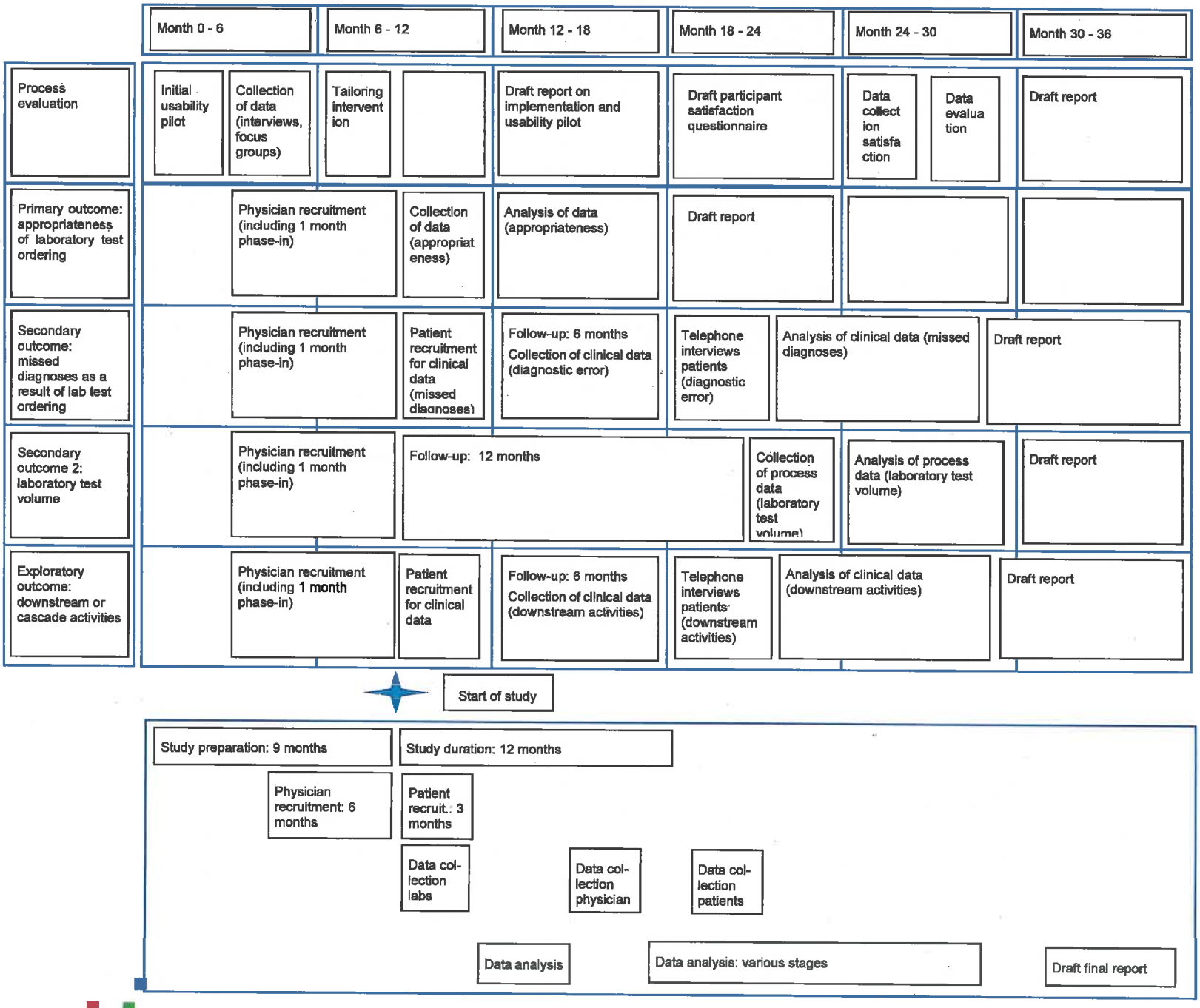

Figure 1: Overview of study and outcomes

STUDY PROTOCOL

The effect of evidence-based order sets within a CPOE (computerised physician order entry) system on the quantity and quality of laboratory test ordering in family practice: a cluster randomised controlled trial.

1 BACKGROUND

Laboratory testing is an important clinical act with a valuable role in screening, diagnosis, management and monitoring of diseases or therapies. Thirty percent of patient contacts in primary care result in ordering of laboratory tests (Cadogan 2015, Hickner 2014). In Belgium, more than 370 million tests are ordered annually implying that for each person about 31 laboratory tests are ordered each year (source: RIZIV-INAMI). Despite the frequency with which laboratory tests are ordered, there is a large variation in the appropriateness of these orders (Driskell 2012, Davis 2002, Laurquin 1995, O'Kane 2011). Inappropriate laboratory test ordering has been estimated to be as high as 30% (Zhi 2013). This seems not to be different in Belgium, where 30 to 50% of tests requested by primary care physicians for the five most common indications were found to be inappropriate in a 2007 KCE study (De Sutter 2007). Besides the burden this poses on health care spending, it may also result in false-positive results and potentially cause excessive downstream diagnostic examinations. The true extent of these downstream diagnostic examinations in primary care have never been thoroughly investigated (Houben 2010).

De Sutter et al (De Sutter 2007) suggested several interventions to influence the test ordering behaviour of physicians including developing evidence-based guidelines, providing feedback, introducing computerized decision support, limiting the amount of tests on the order form, and providing financial incentives. Education-based interventions, feedback-based interventions and clinical decision support systems (CDSS) have shown promising results to influence the test ordering behaviour of physicians and to improve appropriateness (Cadogan 2015). However, these findings tend not to be generalizable because many studies either focus on very limited indications or measure testing volume rather than appropriateness.

Indications for ordering laboratory tests include all the reasons why a physician chooses to order a laboratory test such as diagnosis of complaints, the follow-up of medical conditions, the follow-up of drug or other therapies, preventive care and early detection of adverse effects of a condition or therapy. We will refer to all these reasons for ordering of laboratory tests as *indications*. Our review (Delvaux 2017b) suggested that computerised clinical decision support systems (CCDSS) applicable for multiple indications are more effective than those aimed at a limited number of indications in influencing laboratory testing behaviour, but conclusive evidence is still lacking. *Order sets*, a form of decision support where a limited set of evidence-based tests are proposed for a series of indications, has been shown to be effective in reducing the volume of ordered laboratory tests (Van Wijk 2001, Chan 2012). However, good evidence that the use of order sets aimed at multiple indications improves the appropriateness of laboratory test ordering is still lacking. The aim of this study is to measure the effect of order sets on the quality and quantity of laboratory test orders by physicians.

To evaluate this intervention, we will conduct a cluster randomised controlled trial in Belgian primary care practices. The participants will be primary care physicians working in primary care practices (PCPs) affiliated to one of three collaborating laboratories in the Leuven, Ghent or Antwerp regions. Currently, these laboratories are starting to implement web-based CPOEs integrated in the electronic health record (EHR) of primary care physicians. PCPs will be allocated and randomised to either the intervention or control group. Physicians in PCPs randomised to the intervention will be offered order sets based on indication when using the CPOE for ordering laboratory tests. We will analyse these order sets for 17 common indications for ordering laboratory tests in Belgian primary care.

2 RATIONALE

As our review (Delvaux 2017b) and that of Chan et al (Chan 2012) demonstrated, CDSS in the form of order sets aimed at laboratory test ordering has the potential to improve appropriateness of

laboratory test ordering. However, besides evidence showing that order sets can reduce the volume of laboratory test ordering by 20% (Van Wijk 2001), no sound evidence exists that these interventions improve appropriateness. Moreover, most studies have evaluated the effect of decision support for one or a limited number of indications. Our review could not detect sufficient evidence of effectiveness and suggested that studies with a more comprehensive intervention are necessary.

Such an intervention would need order sets for several indications specifically developed for primary care. However creating, implementing and maintaining evidence-based order sets is a resource intensive activity.

In Belgium, EBM*Practice*Net, a national database of evidence-based clinical practice guidelines has been implemented in 2011 (Van de Velde 2013). This database of over 1000 guidelines has been adapted for use in Belgium and contains recommendations for the majority of conditions or situations experienced by Belgian primary care physicians (Delvaux 2017a). Moreover, the Flemish College of Family Physicians developed guidelines on the laboratory testing for 20 different indications commonly seen in general practice (Avonts 2011, Leysen 2012). This unique database, including the existing national guidelines, provides us with an actual and trustworthy basis for developing a comprehensive series of evidence-based order sets with minimal efforts.

Our research primarily aims to evaluate what the effect is of evidence-based order sets, developed using the clinical practice guidelines available through EBM*Practice*Net, on the appropriateness of laboratory test ordering in primary care. A barrier to adhering to evidence-based policy is the fear for missing important pathology and the liability this may create. There is currently no evidence showing that increasing appropriateness of laboratory testing influences morbidity through diagnostic errors or delay. To evaluate the effect of order sets on diagnostic errors or delay, we will also assess the incidence of potentially missed diagnoses in both the intervention and control groups.

Our previous research suggested that CCDSSs aimed at multiple indications seem more effective than those aimed at a single or few indications (Delvaux 2017b). We will therefore introduce a comprehensive database of order sets aimed at 17 common indications and evaluate the effect of these order sets on appropriateness and on diagnostic error. The rationale for choosing these order sets is discussed in section 5 of this document.

Assuming the intervention is effective in improving appropriateness of laboratory test ordering, we will evaluate whether our intervention is cost-effective. In order to be able to fully evaluate cost-effectiveness we will include the effects of our intervention on test volume and on downstream or cascade activities. Downstream or cascade activities are those medical acts which result from altered or deviant tests. For instance, an elevated liver test in an asymptomatic person has a very high probability of being false positive, but may result in additional testing such as repeat laboratory testing, radiology testing, other technical evaluations or specialist consultations. It is generally assumed that the effects of inappropriate test ordering are larger on the downstream activities than on the tests themselves. This phenomenon is often referred to as the Ulysses effect (Rang 1972). To date, little research has been done on these cascades in primary care and the size of this Ulysses effect is largely unknown (Houben 2010). We would like to gain more insight in these downstream activities and will evaluate these in a small subgroup of patients included in our trial.

2.1 Assessment and management of risk

Our intervention aims to improve adherence to clinical practice guidelines. In theory, our intervention could lead to diagnostic error or delay, however, to date no evidence for this exists. Moreover, exploring this risk is one of the aims of this trial. Our intervention will suggest laboratory tests appropriate for the indication in trustworthy clinical practice guidelines. However these propositions will not be limitative; when the physician deems it necessary to order other or different tests, our intervention will allow for this. Belgian law prohibits clinical laboratories from restricting the number of possible laboratory tests which can be ordered. We therefore assume that any possible risk to our intervention can and will be avoided.

3 OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

3.1 Primary objective

To compare the effect of evidence-based order sets versus control on the proportion of appropriate laboratory tests ordered by primary care physicians on 17 common indications for ordering laboratory tests.

Null hypothesis: evidence-based order sets have no effect on the appropriateness of laboratory tests ordered by primary care physicians compared to control.

Alternative hypothesis: evidence-based order sets will increase the proportion of appropriate laboratory tests ordered by primary care physicians from 70% to 80% compared to control.

Population: tests ordered in patients for 17 common indications by primary care physicians

Intervention: CPOE with evidence-based order sets

Comparison: CPOE without evidence-based order sets

Outcome: proportion of ordered tests assessed as being appropriate for each of the indications

Time: the effect on the outcome is immediate, at the point of care

3.2 Secondary objectives

3.2.1 Diagnostic error

To demonstrate non-inferiority in the effect of evidence-based order sets versus control on the incidence of missed or delayed diagnoses for 17 common indications by primary care physicians.

Null hypothesis: evidence-based order sets increase the incidence of missed or delayed diagnoses in primary care by more than 1%.

Alternative hypothesis: evidence-based order sets do not worsen the incidence of missed or delayed diagnoses by primary care physicians compared to control, i.e. $pA - pB < 1\%$, with pA and pB being the proportion of missed diagnoses in the intervention and control groups, respectively.

Population: patients for which laboratory tests were ordered for 17 common indications by primary care physicians

Intervention: CPOE with evidence-based order sets

Comparison: CPOE without evidence-based order sets

Outcome: incidence of missed or delayed diagnoses related to the 17 indications

Time: continuously during 6 months following initial laboratory test ordering

3.2.2 Test volume

To compare the effect of evidence-based order sets versus control on the number of laboratory tests ordered by primary care physicians with no restriction on the indications.

Null hypothesis: evidence-based order sets have no effect on the number of laboratory tests ordered by primary care physicians compared to control.

Alternative hypothesis: evidence-based order sets decrease the number of laboratory tests ordered in primary care by 20%.

Population: tests ordered by primary care physicians without restriction on indications

Intervention: CPOE with evidence-based order sets

Comparison: CPOE without evidence-based order sets

Outcome: amount of ordered tests

Time: immediate, at the point of care

3.3 Outcome measures/endpoints

3.3.1 Primary endpoint/outcome

The definition of (in)appropriateness is broad and can be interpreted in various ways. Zhi et al state four ways of understanding inappropriateness (Zhi 2013):

- Restrictive: a test is considered inappropriate if there is no clear indication for ordering the test. For instance, if for condition A, 5 tests are considered appropriate, then all additional tests are considered inappropriate.
- Permissive: a test is considered inappropriate if there is a clear indication for not ordering the test. If this is not the case, the test is considered appropriate, even if no good indication for ordering the test is provided. For instance, if for condition A, 5 tests are not indicated, only these tests are considered inappropriate. All other tests will be considered appropriate.
- Overutilization: a test is considered inappropriate if it is ordered too often for the given condition. For instance, if for condition A, a test X is considered appropriate when it is ordered once per year, then all additional tests X in the same year will be considered inappropriate.
- Underutilization: a test is considered inappropriate if it is not ordered within a certain time frame for a given condition. For instance, if for condition A, a test X is considered appropriate if it is ordered once per year, than all missing tests X in that year will be considered inappropriate.

In our study all ordered tests that are not indicated will be considered as inappropriate (restrictive definition) as well as tests that are indicated but not ordered (underutilization).

3.3.2 Secondary endpoints/outcomes

3.3.2.1 Diagnostic error

Due to the role of the GP as a gateway keeper, caring for a variety of complex patients, he is vulnerable to diagnostic errors (Kostopoulou 2008). Diagnostic errors are defined as diagnoses that were unintentionally delayed, wrong or missed (Graber 2005). In a classification of diagnostic error, amongst the most important reasons for diagnostic error in laboratory testing were the failure or delay in ordering needed tests and ordering of the wrong tests (Schiff 2009). Previous studies (Hickner 2014) have shown that fear of malpractice or liability influences the test ordering behaviour of physicians. Despite the vulnerability of primary care for diagnostic error, incidences remain low. Very little reliable figures on diagnostic error due to laboratory testing exist, but several studies estimate it less than 0.1% (Singh 2013) to 2.5% (Paneshar 2015). An important concern in the interpretation of these results lies in the fact that they are often based on retrospective analyses with hindsight bias (Zwaan 2013). Despite these apparently low figures, fear of diagnostic error (and related liability) is an important concern for physicians when ordering laboratory tests (Hickner 2014). Our secondary aim is to demonstrate that improving appropriateness of laboratory testing does not result in more diagnostic errors.

To date, there is no standardised way of measuring diagnostic error. The Core Outcome Measures in Effectiveness Trials (COMET) initiative has no registered outcomes concerning diagnostic error and no guidelines on how to detect diagnostic error exist (www.comet-initiative.org). The review by Kostopoulou et al (Kostopoulou 2008) analysed studies on diagnostic delay of solitary conditions. All of the included studies were retrospective studies looking backward at the medical history of patients with the same diagnosis and analysing the (delay in the) diagnostic process preceding the diagnosis. Singh et al (Singh 2013) used a novel approach to defining diagnostic error through creating an

electronic health record-based trigger on patterns of patient's unexpected return visits after an initial primary care index visit. This trigger appeared to have worked well, however an important note was that this trigger depended on both primary care and secondary care visits being recorded in the same EHR. This is not the case in our setting. Recent research on study designs to evaluate diagnostic error proposes the EHR as gold standard for measuring this outcome as it offers the best longitudinal overview of the diagnostic process for a patient (Zwaan 2013). However, no sound evidence exists that the EHR is capable of capturing all causes of diagnostic error. As we are unable to rely upon previous research to define and measure diagnostic error, we will construct a new method.

We will define *diagnostic error* as *a diagnosis that was unintentionally delayed (sufficient information was available earlier), wrong (another diagnosis was made before the correct one) or missed (no diagnosis was made)*, in accordance with the definition of diagnostic error by Graber et al (Graber 2005). Our order sets recommend tests for initial testing (when a condition or disease is suspected) or for monitoring (when a condition or disease has been diagnosed, but follow-up for the early detection of potential side-effects of treatment or to monitor the evolution of the condition is warranted). In both situations the potential for diagnostic error is present. To illustrate this definition we present several examples.

Example of diagnostic error in initial testing (wrong test):

> A physician suspects that his patient, who presented with a swollen knee, suffers from an acute attack of gout. He decides to test his patient for plasma uric acid to confirm his suspicion. Plasma uric acid levels are elevated, apparently confirming his suspicion and he prescribes the patient a non-steroidal anti-inflammatory drug. Several days later, the patient returns with fever, increased swelling of the knee and intensified pain. The physician aspirates some synovial fluid and notices pus in the sample. The patient did not suffer from a gout attack but from a septic arthritis. A diagnostic aspiration of synovial fluid would have diagnosed the condition earlier.

Example of diagnostic error due to not testing:

> A female patients consults with general fatigue. The GP, knowing that the patient has a stressful life, explains the fatigue as a reaction to this stress. He considers laboratory testing not relevant in this case. A few months later the patient is diagnosed with hypothyroidism.

Example of diagnostic error due to superfluous testing:

> A young adult patient consults because of decreased power during his weekly football training. The GP performs a laboratory test which shows increased Epstein-Barr antibodies (EBV-IgG). The GP ascribes the complaints to a recovering mononucleosis infection and misses the real reason for the complaints, which is overtraining. EBV-IgG indicates an old infection and has no diagnostic value in this case but led the GP to a wrong conclusion.

Example of diagnostic error in follow-up testing:

> A patient consults his physician for a yearly check-up of hypertension for which he has been prescribed a thiazide diuretic. The physician checks his blood pressure and finds it well controlled. He confirms the treatment and prescribes refills without performing any laboratory tests. Several weeks later, the patient consults the emergency room because of a sudden syncope. In the hospital, the physicians note that he suffers from a hypokalaemia due to the thiazide treatment. This is an example of a missed diagnosis that should have been made during the yearly check-up of the hypertension treatment.

Measuring this outcome is a challenge. We tested the idea of introducing an automated extended audit in order to identify certain pathologies or events directly from the EHR, but this poses several

problems. First, primary care physicians work with a broad variation of EHR software systems. Not all of these systems are capable of performing extended audits, and those who are have different ways of executing audits. This would result in several variations of the same automated audit and has repercussions on validity and reproducibility. Second, not all data in the EHR is sufficiently structured to be able to include in an automated audit. It is also possible that a delayed diagnosis is not made by the primary care physician, but instead by a specialist after referral. Elements of a specialist report are not structured elements within an EHR, therefore we believe that an automated audit will not be sufficiently sensitive to detect diagnostic error.

Self-reporting is another possible way of measuring diagnostic error, but an important barrier here is the observation that relying solely on physicians to report events that indicate diagnostic error is often insufficient as physicians may very well be reluctant to share or judge their own missed or delayed diagnoses due to fear of malpractice litigation (Schiff 2009).

Chart review, the gold standard, also has limitations as it will often only detect those missed diagnoses that resulted in a return visit or unexpected hospitalization. Less harmful missed diagnoses may not be detected through these methods.

To ensure a sufficiently sensitive and specific methodology for detecting this outcome we will use a stepped approach, combining physicians' reporting of events, chart review and direct patient interviews of a sample of patients.

1. For each included panel we will notify the study physician that his patient is included in the trial and request that he reports all clinical diagnoses (irrespective of whether they could be considered as "errors") or clinical events that this patient experienced during the whole study period of six months.
2. The study physicians will be reminded at regular intervals to report any new diagnoses or events for the included patients until the end of the study period.
3. Structured elements such as problem lists and new diagnoses will be extracted from the EHR through an automated audit.
4. All clinical diagnoses will be reviewed by two researchers independently for cases of potential diagnostic error. For this purpose a list of criteria will be composed (e.g. it must be possible to suspect or diagnose the condition using laboratory tests). In cases of disagreement a third reviewer will be consulted. Interrater agreement will be calculated and reported.
5. To check the completeness of the data, patients will be telephoned for additional information. In case of doubt, the evaluation of the telephone interview will be reviewed by a second researcher.

The rationale for step 5 of this process is that some diagnostic errors do not result in additional visits, further investigations, or change in practice and will not be recorded in the EHR. Interviewing the patient is the only way to detect these diagnostic errors. This part of the study will allow us to test the hypothesis that review of the EHR is the gold standard for measuring diagnostic error. We plan to interview around 565 patients: approximately 315 patients with a case of diagnostic error (assuming a 2.5% rate of diagnostic error) and 250 patients for which no case of diagnostic error was reported.

The outcome will be measured as the number of diagnostic errors in each arm.

3.3.2.2 Test volume

We will also evaluate the effect of evidence-based order sets on test volume. Zhi et al (Zhi 2013) suggest that inappropriateness is not only a result of overutilization but also of underutilization and that improving appropriateness may not necessarily result in reducing test volume. We will measure this outcome to add data to this discussion. Measuring test volume for each of the study indications will also allow to measure the sustainability of the intervention over time. Measuring test volume over time for all laboratory tests ordered by physicians will allow us to estimate an overall effect of the use of order sets on laboratory test volume.

This outcome will be measured as the number of tests ordered in each arm for the 17 indications individually and for all laboratory tests ordered by physicians.

3.3.3 *Exploratory endpoints/outcomes*

We will attempt to assess the effect of our intervention on the downstream activities arising from abnormal results of inappropriate tests. A full description of this assessment can be found under 8.9.3.

Objectives	*Outcome Measures*	*Timepoint(s) of evaluation of this outcome measure (if applicable)*
Primary Objective: • **To compare the effect of evidence-based order sets versus control on the proportion of appropriate laboratory tests ordered by primary care physicians**	**Primary Objective:** • We will evaluate the effect of 17 order sets on the appropriateness of laboratory tests. This will be measured for all tests collected from 300 physicians over a period of 3 months	**Primary Objective:** • Data collection from the LIS 3 months after the start of the study
Secondary Objectives: • **To compare the effect of evidence-based order sets versus control on diagnostic error by primary care physicians** • **To compare the effect of evidence-based order sets versus control on the amount of laboratory tests ordered by primary care physicians**	**Secondary Objectives:** • We will evaluate the effect of 17 order sets on diagnostic error • We will compare volume of laboratory tests for each indication. We will also continue to monitor test volume after the intervention period in both the intervention and control arms	**Secondary Objectives:** • We will continuously survey study physicians during the study. Responses by physicians will be verified through review of data extracted from the HER • We will extract laboratory test volume data from the LIS at 6 months and 12 months after the start of the study

Table 1: Summary of primary and secondary objectives, outcomes and time points of evaluation

4 STUDY SETTING

The study will be situated in Belgian family practice. We estimate that about 124 PCPs will be included in the study (300 physicians working in 124 different PCPs). The targeted professionals are active family physicians. The study will be conducted in practices collaborating with one of three private laboratories:

1. **MCH** (Medisch Centrum Huisartsen, Maria Theresiastraat 631, 3000 Leuven),
2. **Anacura** (Noorwegenstraat 4, 9940 Evergem), or
3. **AML** (Algemeen Medisch Laboratorium, Emiel Vloorsstraat 9, 2020 Antwerpen).

These laboratories collaborate with physicians throughout Flanders, primarily located in the region of Leuven/Flemish Brabant (MCH), East- and West-Flanders (Anacura) and Antwerp and East-Flanders (AML). Both MCH and Anacura provide laboratory services to around 500 primary care physicians, whereas AML delivers services to about 1000 physicians. All laboratories cooperate primarily with primary care physicians, but in a much smaller amount also with some private specialist practices. The study will be conducted amongst family physicians prepared to change their laboratory testing ordering from paper-based to an online CPOE.

Currently around 30% of collaborating physicians use the laboratory CPOE to order laboratory tests (personal communication 2016). All other physicians use a paper-based order form to order tests. The paper-based order forms consist of a selection of common (and less common) laboratory test, often ordered by type, such as chemistry, microbiology, haematology, etc. Figure 2 illustrates a paper-based laboratory form. An important goal will be to be able to include physicians naïve to the use of CPOE. See 8.1 for our strategies to maximise recruitment of physicians.

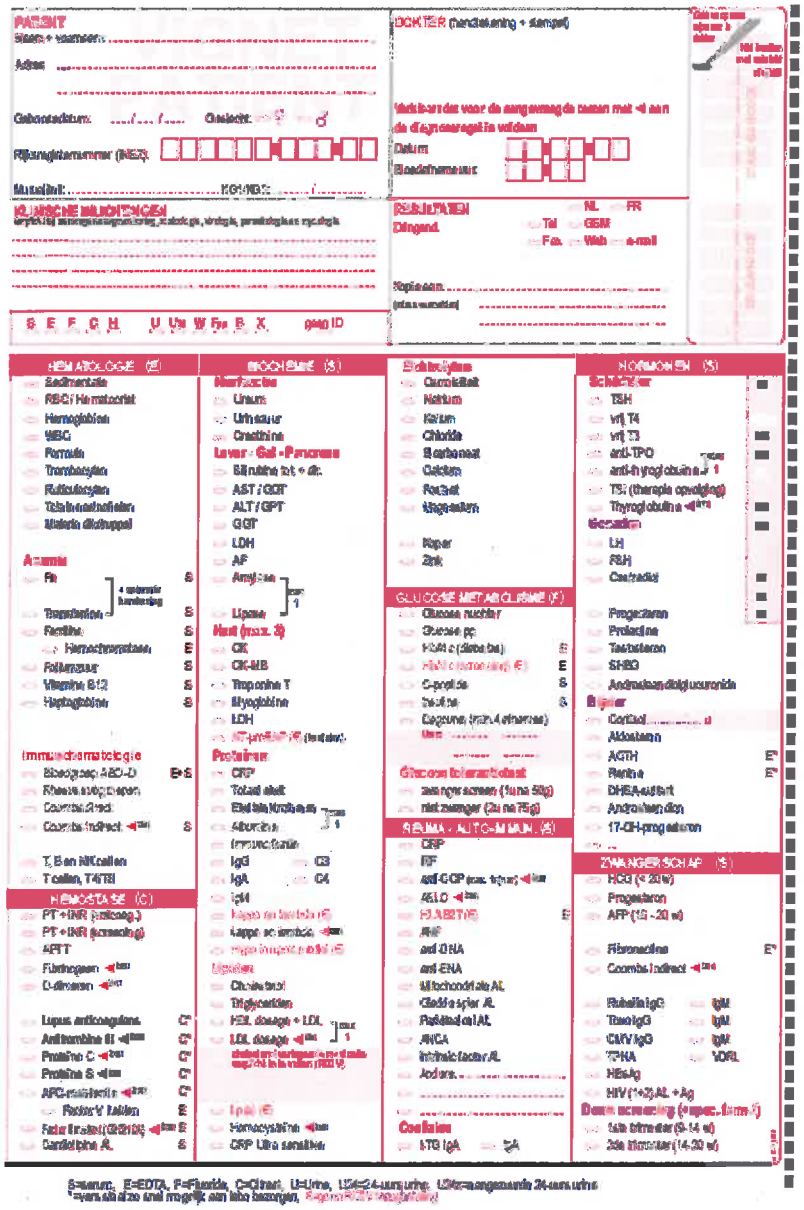

Figure 2: Example of a paper-based laboratory order form.

The study by De Sutter et al (De Sutter 2007) showed that for a series of five key tests (ureum, total protein, amylase, thrombocytes, and chloride), inappropriateness was as high as 77.5 or even 100%. For these tests, the prevalences (measured as the number of test panels including one of these test over the total number of test panels) found in their study are similar to those found at the three collaborating laboratories (data from 2016). Table 2 summarizes these prevalences. On average physicians order 14.61 tests per panel at AML, 14.2 tests at Anacura and 14.25 tests at MCH (personal communication). In the study by De Sutter et al, the average amount of tests per panel was similar, at 13.3 tests (De Sutter 2007).

Test	Prevalence De Sutter et al (in %)	Inappropriateness De Sutter et al (in %)	Prevalence Anakura (in %)	Prevalence MCH (in %)	Prevalence AML (in %)
Ureum	25.3	87	28.65	36.35	34.40
Total protein	17.5	100	15.08	12.58	18.30
Amylase/Lipase*	13.7	77.5	14.28	15.03	13.31
Thrombocytes	52.8	95	53.87	55.12	51.19
Chloride	16.7	100	20.68	27.02	24.38

Table 2: Comparison of prevalences between 5 key tests in the study by De Sutter et al (De Sutter 2007) and the prevalences of the same tests in the three collaborating laboratories in 2016. Prevalences are measured as the amount of panels including the test over the total number of panels. *In the study by De Sutter et al (De Sutter 2007), only amylase was measured. Since then a rule was introduced limiting the possibility to order both amylase and lipase at the same time. In the prevalences for the collaborating laboratories, the combined prevalence for amylase and lipase was measured.

5 TRIAL INTERVENTION

5.1 Name and description of intervention

Currently, most laboratory test orders are done through a paper-based system. Physicians request or take a blood sample from a patient, order tests manually on a paper form by ticking boxes next to each wanted test (Figure 3: Screenshot of EHR with link to CPOE), manually add the patient contact detail to the form and send both the form and the test tubes in a plastic bag to the laboratory. This paper form makes the integration of decision support very difficult. Integrating order sets of problem-oriented laboratory orders would result in very large order forms.

Slowly, ambulatory laboratories in primary care have started adopting CPOEs for ordering laboratory tests. CPOEs have several benefits for both laboratories and physicians:

- Reduces mistakes during the pre-analytical phase;
    - patient contact information, insurance status;
    - handling of samples, amount and types of samples to correctly perform requested tests;
    - reduces manual or semi-automatic handling such as scanning of paper-based orders, manually transcribing orders into LIS;
- Improves timeliness of reporting (Westbrook 2006);
- Reduces mistakes during additional orders on same sample;
- Reduces overall turn-around time of samples (Thompson 2004);

The adoption of CPOEs also provides perspectives in providing computerized clinical decision support. One form of decision support is the integration of predefined order sets, proposing a set of evidence-based laboratory tests for a series of common indications.

The intervention being evaluated in this study is a CPOE with integrated order sets.

We will use two different types of CPOE in our study:

1. LabOnline (Moonchase) implemented at AML and MCH, and
2. E-Lab implemented at Labo Anacura.

Both systems are online platforms that allow the ordering of laboratory tests and the review of lab results through a web-based interface. They are linked to the EHR and integrate patient contact details through an XML message. To date, no patient-specific medical data is shared between the EHR and the CPOE. When a physician initiates a laboratory test order through the EHR, a web browser is opened which allows the physician to order laboratory tests.

Currently, users are guided to an overview of commonly used laboratory tests, very much like a paper-based form. In our intervention, physicians will be prompted to enter the indication(s) for ordering laboratory tests through a searchable drop-down menu of common indications (E-Lab,Figure 8) or a list of indications which can be selected through tick-boxes (LabOnline, Figure 4). Selecting one or more of these indications will prompt a new window where the appropriate tests for these indications are shown as being ordered (E-lab, Figure 9 and LabOnline Figure 5 and Figure 6). In this window, the user will be able to accept the panel as it is or to cancel one or more of the ordered test or to add tests (LabOnline, Figure 7). The user will not be restricted in ordering any tests, but will be 'nudged' in the direction of ordering only the appropriate tests.

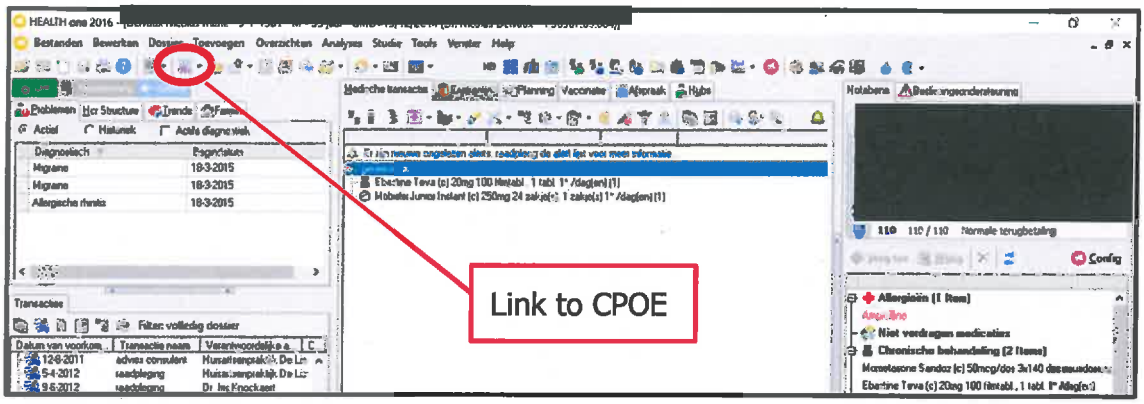

Figure 3: Screenshot of EHR with link to CPOE

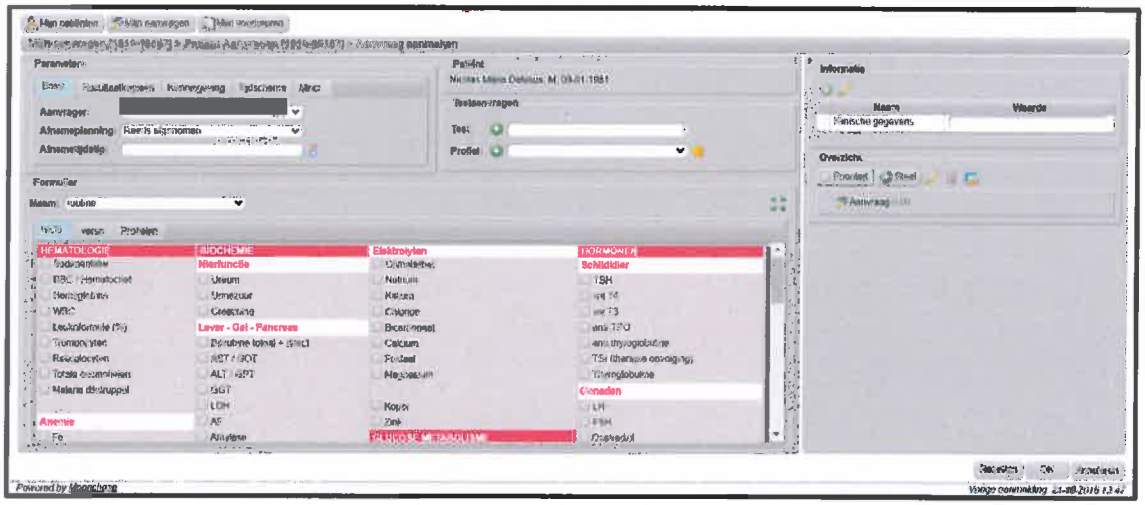

Figure 4: Screenshot of LabOnline (Moonchase)

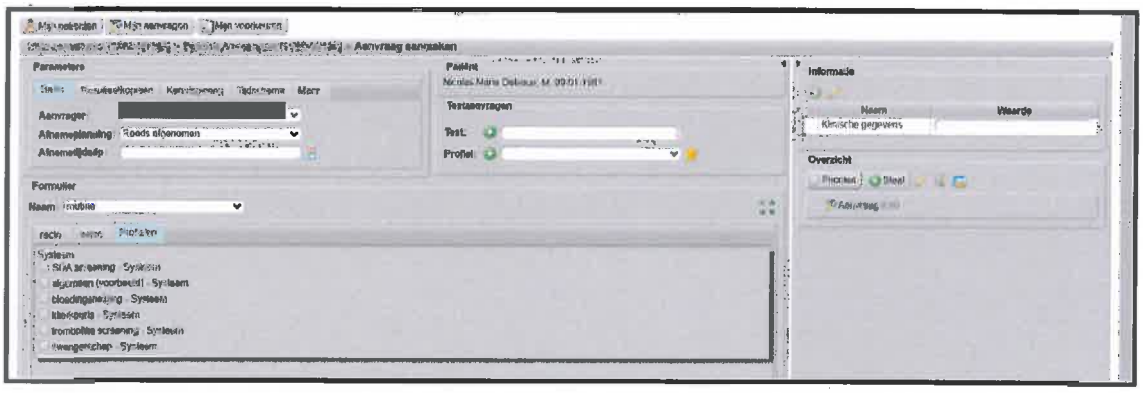

Figure 5: Screenshot of sample order sets (named 'profielen') in LabOnline

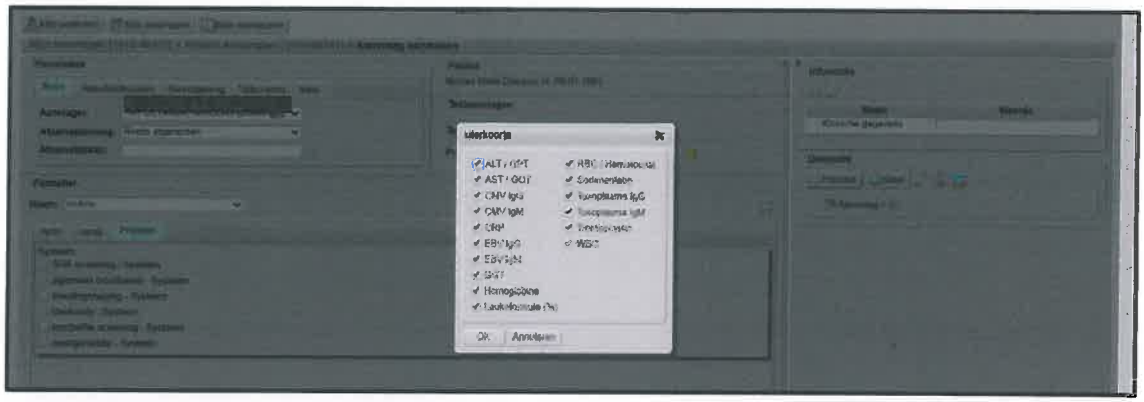

Figure 6: Screenshot of overview of tests which are ordered when selecting an order set in LabOnline

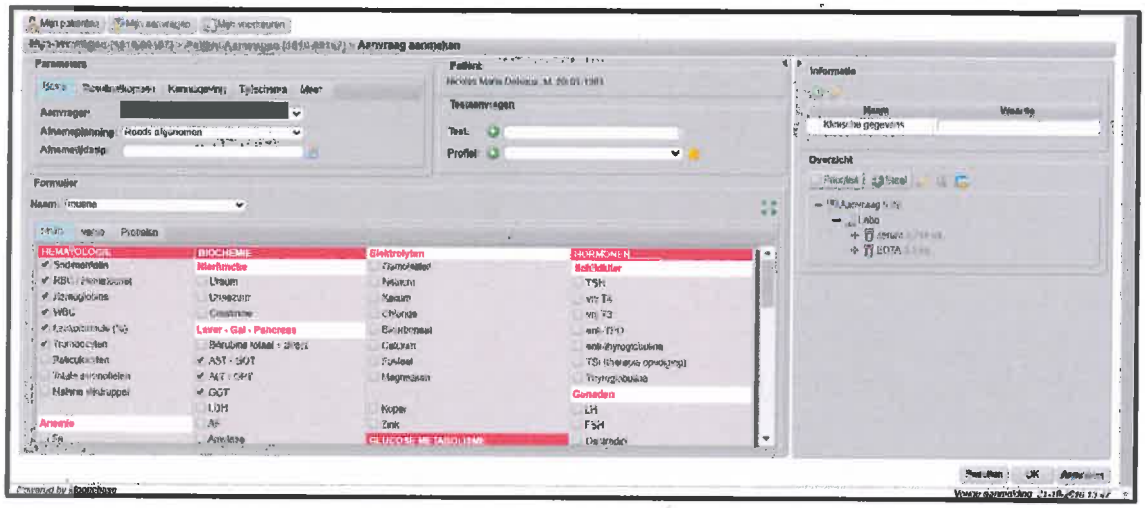

Figure 7: Screenshot of overview of laboratory test order, allowing the physician to remove or add additional tests to the order in LabOnline

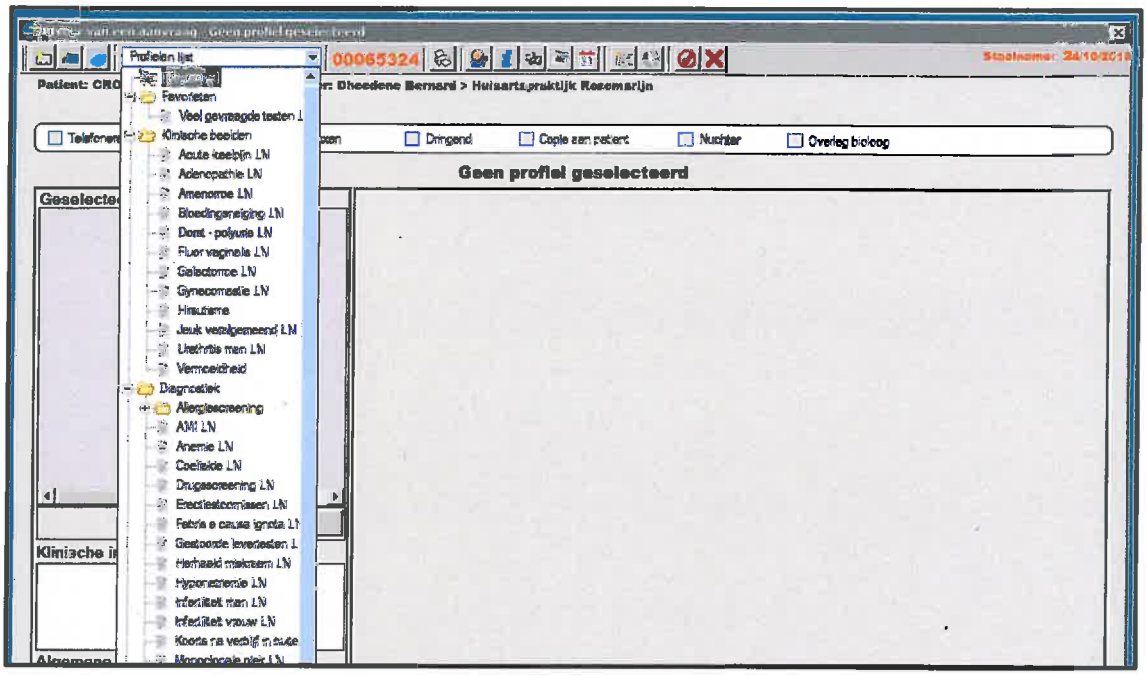

Figure 8: Dropdown list of order sets (named 'profielen') in E-Lab

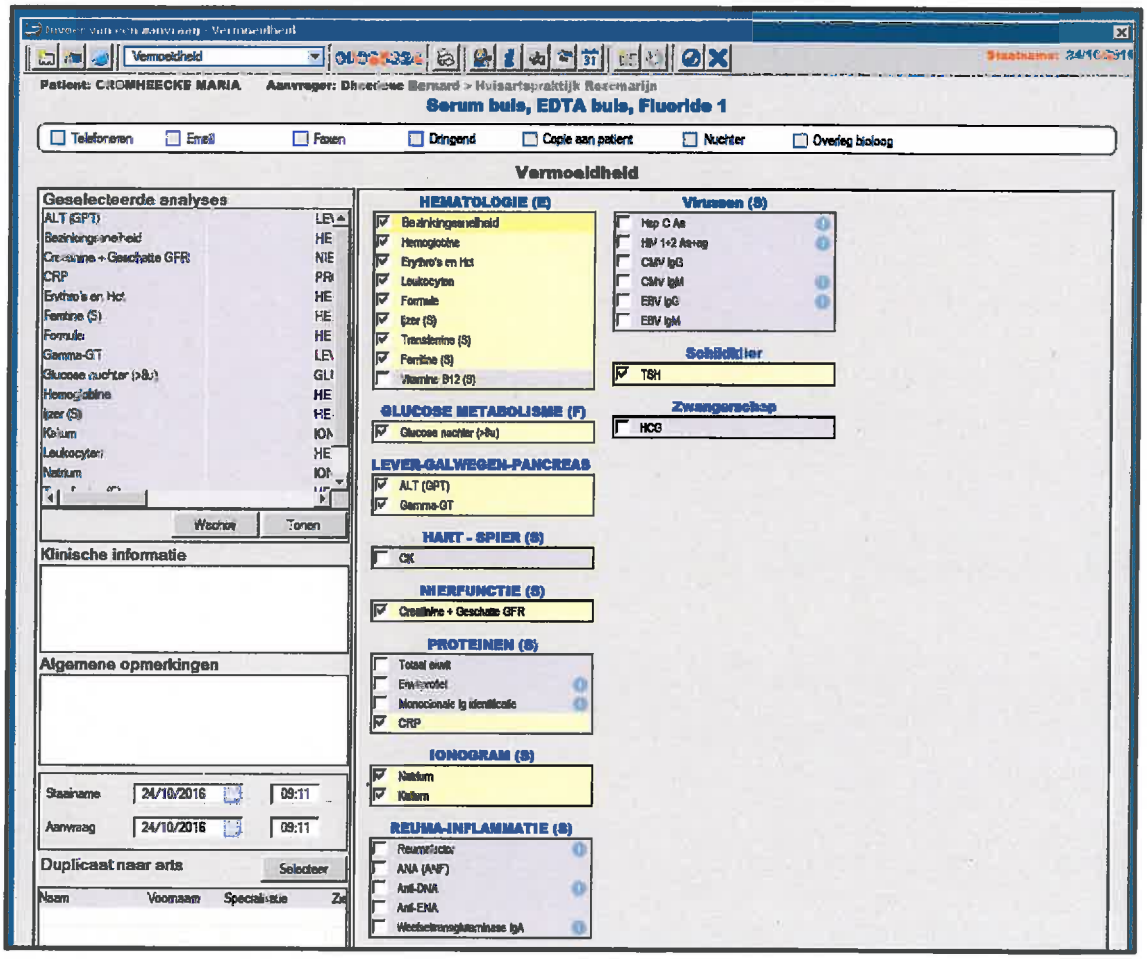

Figure 9: List of proposed tests for order set including additional optional tests in E-Lab

At the start of our intervention, all physicians will have been allocated to either the intervention or the control group. When accessing the CPOE, the intervention physicians will be able to select the indication(s) from a drop down menu or from a list of tick-boxes. The selection one or more of these indications will result in a laboratory order form with preselected tests. At this stage the physician will be able to add or remove tests from the final order.

Because we are dependent on the physician recording the indication of the laboratory test order to determine appropriateness, he will be prompted to enter an indication if he has failed to do so before validating the order. Physicians in the control group will follow the same procedure, but entering an indication will not result in any preselected tests, instead the physician will be presented with an empty order entry form. In case the control physician has failed to enter a diagnosis, he will be prompted to do so before validating the order.

Physicians will still be able to order laboratory tests through the paper-based form as alternative to the CPOE, especially in situations where there is no computer or internet connection available such as during house-calls.

5.2 Choice of order sets for evaluation

We considered several criteria when choosing the indications for which we will present order sets.

1. Frequency: we chose the indications with the highest testing rate. High volume indications will result in larger effects in a shorter study period, whereas low volume indications will show an effect over a larger period of time. The study by De Sutter et al (De Sutter 2007) and the study by Janssens et al (Janssens 2012) allowed us to identify indications with high testing frequencies.
2. Baseline inappropriateness: we also considered the potential for improving appropriateness. Indications for which evidence suggests that there is little inappropriate testing are less interesting for our study. However, to date, we have no reliable data on this. The study by De Sutter et al (De Sutter 2007) identified some indications that lead to inappropriate testing, in some cases as high as 60%.
3. Trustworthy guidelines: the availability of trustworthy guidelines to underpin the selection of tests for a suspected condition or complaint was a prerequisite for developing order sets. Therefore we excluded indications for which no clinical practice guidelines were available on the EBM*Practice*Net platform, when the guidelines were ambiguous or when tests were advised that are not reimbursed in Belgium.
4. Potential for diagnostic error: an important concern was including sufficient indications that could potentially lead to diagnostic error. We used the taxonomy from Singh et al (Singh 2013) to include indications or complaints that were found to have led to diagnostic error.

We chose to assess the effect of the order sets for 17 different indications (Table 3), based on the above criteria.

Frequency: it is unknown what proportion of all laboratory panels these 17 indications represent, but the study by De Sutter et al (De Sutter 2007) showed that five of these 17 accounted for almost 40% of all laboratory panels. These five indications were general check-up, diabetes, hypertension, fatigue and cardiovascular screening. See Appendix 2 for the full list of order sets being studied.

Baseline inappropriateness: the study by De Sutter et al (De Sutter 2007) measured baseline inappropriateness for the five most frequent indications and found 38 to 60% of ordered tests to be inappropriate. We have no baseline data for other indications, but included these five indications in our order sets.

Trustworthy guidelines: the Flemish College of Family Physicians have developed guidelines on laboratory testing for 19 different indications (Avonts 2011, Leysen 2012). We chose to add one additional indication, general check-up, because this is a very frequent reason to test as shown in the study by De Sutter et al (De Sutter 2007) and leads to high rates of inappropriate testing. This order set, meant for patients with no complaints, includes tests for cardiovascular risk evaluation and,

for elderly patients, TSH and aims to reduce inappropriate testing for this specific indication. We also chose to exclude one indication: follow-up of international normalized ratio (INR). Despite being prone to under-testing, this has already been thoroughly researched (Claes 2005). Additionally, order sets for follow-up of pregnancy and heart failure were not included because of ambiguity of the recommendations or presence of not-reimbursed tests.

Potential for diagnostic error: The remaining 17 indications for testing were, with the exception of two (obesity and thyroid disease) all associated with cases of diagnostic error in the study by Singh et al (Singh 2013).

	Indication	Included in Flemish guidelines*	Included in study by Singh et al†
1	**Cardiovascular disease**	Yes	Yes
2	**Hypertension**	Yes	Yes
3	**Diabetes mellitus**	Yes	Yes
4	**Anemia**	Yes	Yes
5	**Liver pathology**	Yes	Yes
6	**Medication monitoring**	Yes	Yes
7	**Gout**	Yes	Yes
8	**Chronic kidney disease**	Yes	Yes
9	**Lung embolism**	Yes	Yes
10	**Acute coronary syndrome**	Yes	Yes
11	**Diarrhea**	Yes	Yes
12	**Thyroid disease**	Yes	No
13	**Unexplained fatigue**	Yes	Yes
14	**Sexually transmitted disease**	Yes	Yes
15	**Rheumatoid arthritis**	Yes	Yes
16	**Obesity**	Yes	No
17	**General check-up**	No	Yes

Table 3: The 17 indications or complaints being assessed. *All indications except 'general check-up' were included in the Flemish guidelines on laboratory testing (Avonts 2011, Leysen 2012). †All indications except 'thyroid disease', 'pregnancy and preconception diagnostics' and 'obesity' were identified as indications associated with diagnostic error in Singh et al (Singh 2013).

5.3 Development of decision support tool

We have developed a series of order sets based on recommendations available through the EBM*Practice*Net platform, a national database of point-of-care, summarized guidelines (Van de Velde 2011, Delvaux 2015a). We have chosen this database because it contains context-specific guidelines on more than 1000 conditions or situations from which we extracted recommendations on more than 60 indications, conditions or situations. Moreover, it includes all the evidence-based guidelines produced by Belgian EBM organisations, including the guidelines on laboratory testing developed by the Flemish College of Family Physicians (Avonts 2011, Leysen 2012).

Before the start of the trial these order sets will be translated into a decision support tool that suggests a panel of recommended tests when the physician records the indications or conditions for testing. Translating these recommendations into an information technology tool can be influenced by multiple factors and the success of these decision support tools is strongly dependent on these (Van de Velde 2016). To avoid implementation errors in designing our intervention, each of the order sets and their integration into the CPOE as a CCDSS will be analysed for usability with physicians, clinical biologists and information technologists and tested in a small subset of physicians (see 8.9.1 for a full description of the implementation process evaluation). The CPOE with order sets will be analysed and improved using the GUIDES checklist as reference (Van de Velde 2016). 17 order sets will be introduced as intervention and evaluated (Table 3).

5.4 Assessment of compliance

Physicians will have the choice to use the paper-based order forms or the CPOE to order laboratory tests. To date, about 30% of physicians use the CPOE for routine ordering of laboratory tests in the three collaborating laboratories, and some physicians have already developed their own personal order sets. We will target physicians who have not previously used order sets but without restrictions concerning proficiency in the use of a CPOE. The rationale for this choice is to include physicians with average 'eHealth literacy' making our results more generalizable. We will measure their compliance throughout the trial period by monitoring the amount of paper-based orders. When a rise in the amount of paper-based orders is noticed for a study physician, he will be contacted by the laboratory or a research assistant to encourage further use of the CPOE.

6 TRIAL DESIGN

Our trial will be designed as a cluster randomised controlled trial and powered as a superiority trial for our primary outcome. For the secondary outcome, the trial will seek to establish non-inferiority. The trial will have sufficient statistical power for both outcomes and will include of a three month intervention period and a six month follow-up period.

Six months after the end of the intervention period, all participants will receive our intervention and we will continue to measure appropriateness and volume of testing in a prospective observational design in the original intervention group as a measure of sustainability.

We will randomize participating PCPs to the intervention or to a control group. The unit of allocation is the PCP. This means that all physicians in the same practice will be allocated to the same intervention and that either all or no physicians in the PCP will be included in the trial. All patients cared for by the same primary care practice will be exposed to the same intervention. In this description, we assume the recruitment of 300 physicians. In the case where less physicians are recruited, we will use an adaptive design as described in Appendix 3.

6.1 Cluster randomised controlled design

During a period of nine months, 150 intervention physicians will be exposed to our intervention and 150 control physicians will not. After these nine months, all physicians will be exposed to our intervention. Three months are sufficient to measure the effect of our intervention on a significant amount of patient contacts and laboratory test orders, and data on appropriateness will be collected at three months. At nine months, and after the data collection for diagnostic error, all study physicians will receive our intervention. Figure 10 illustrates the flow of the study with a sample of at least 300 physicians.

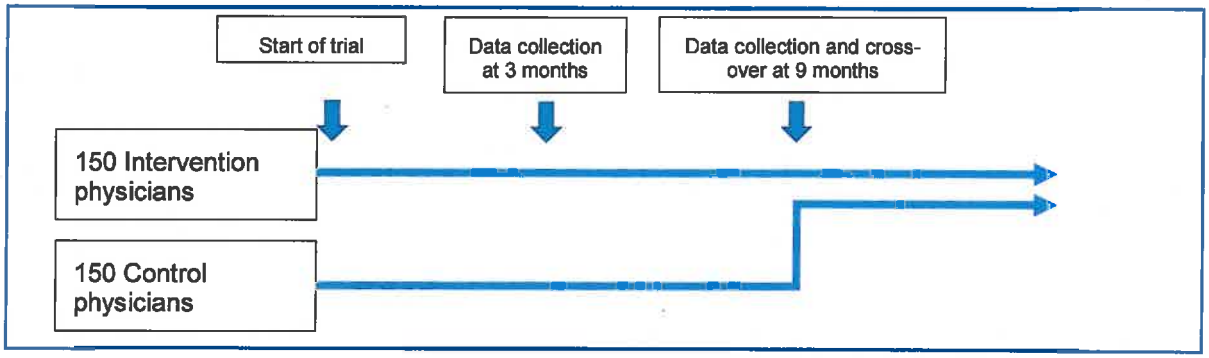

Figure 10: Flow of trial for appropriateness for sample of 300 physicians.

6.2 Follow-up after cross-over

After the nine month trial period, all physicians will be exposed to the intervention for an additional three months (this is further referred to as the cross-over at 9 months). For the physicians in the intervention group, this will allow us to evaluate the sustainability of our intervention on laboratory test volume in a prospective observational design. We will continue to monitor appropriateness and volume for a total period of twelve months. Figure 11 illustrates the trial with the initial intervention period and the observational period of 1 year after the start of the trial.

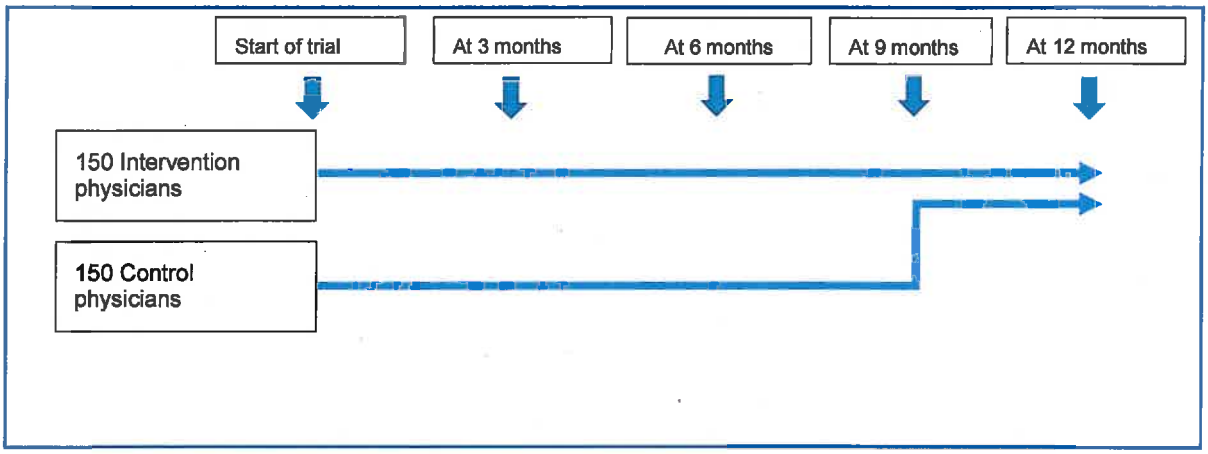

Figure 11: Flow of the trial for volume of laboratory tests for sample of 300 physicians.

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

PCPs will be considered eligible if all the physicians active in the practice agree to be involved in the study. PCPs where one or more physicians refuse to be enrolled will be excluded.

All family physicians will be considered eligible if they:

- Collaborate with either MCH, Anacura or AML for their laboratory test orders,
- Agree to use the online CPOE for their laboratory test orders,
- Use a computerized EHR for patient care,
- Have little or no experience in the use of order sets within a CPOE,
- Agree to the terms in the clinical study agreement.

We will aim our recruitment primarily at physicians with no prior experience in the use of order sets. The rationale for this exclusion criterion is that physicians who already use some form of order sets will not stop doing so if they were to be allocated to the control group. Experience in the use of a CPOE will not be an exclusion criterion as we wish to include physicians with varying experience in the use of IT.

7.2 Exclusion criteria

No physicians will be excluded on other grounds than the above. Age, demographics, prior use of a CPOE (without the use of order sets), prior laboratory ordering behaviour, etc will not be used to exclude eligible physicians. This will provide us with a real-life, representative subset of family physicians.

8 TRIAL PROCEDURES

A detailed breakdown of the various stages of the trial are presented in Figure 12. Figure 13 shows a detailed overview of each stage of trial and the various data collection points. Appendix 3 details the adaptive situation in case of a smaller sample of physicians.

Trial procedures in case of a sample of 300 physicians (150 physicians per arm)
Month 0-9 : participants involved designing and tailoring of the intervention, installing and configuring CPOE platforms, including usability testing, debugging and adjusting problems
Month 3-9 : physician recruitment
Month 8 : phase-in period of 1 month
Month 9 : start study
Month 9-12 : intervention period (data collection for appropriateness and test volume)
Month 12 : data collection for appropriateness and test volume
Month 12-18 : analysis data for appropriateness
Month 12-18 : follow-up of included patients
Month 15-18 : data collection through HD4DP for possible diagnostic error (directly from study physicians)
Month 18-21 : telephone interviews of participating patients for data collection for diagnostic error and downstream activities
Month 18-28 : analysis of data for diagnostic error and downstream acitivities
Month 28-35 : drafting of reports on primary and secondary outcomes

Figure 12: Trial procedures in case of sample of 300 physicians.

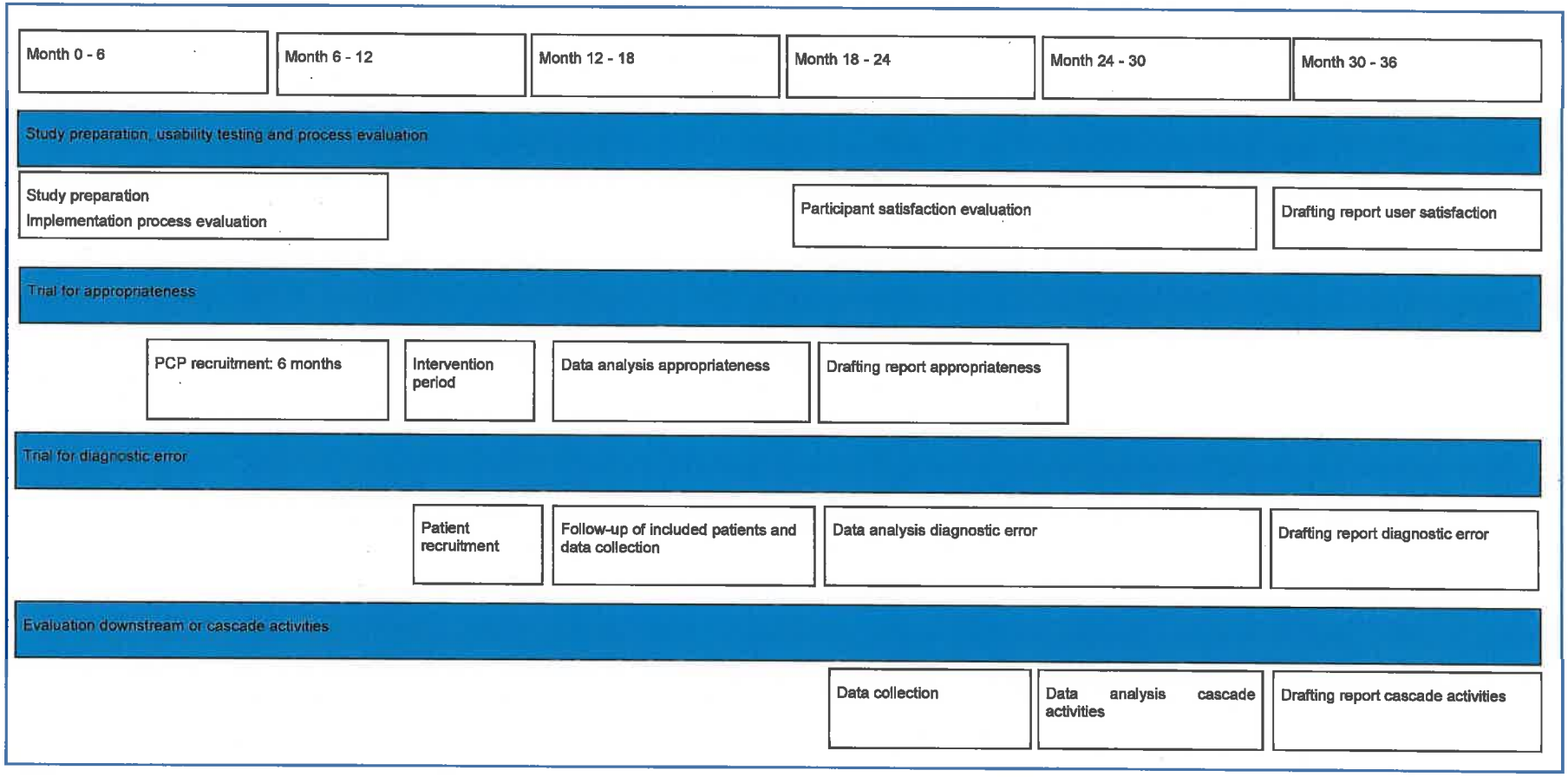

Figure 13: Overview of trial procedures.

8.1 Recruitment

As our intervention is aimed at physicians, we will recruit physicians for our study. We will aim our recruitment efforts primarily at physicians with no prior experience with order sets and the use of a CPOE (see section 315.4).

Recruiting physicians rather than patients, is a strategy that has been used in previous cluster RCTs and has been deemed exempted from patients' informed consent (Heselmans 2013). However, we will be including patient data to assess the effectiveness of our intervention. Therefore we will ask all included patients for consent that their patient data be shared with the research facility, using the informed consent form (ICF) model for observational studies (Appendix 1.1). See 8.2 for a detailed description of our consent procedure.

We will invite all physicians collaborating with MCH, Anacura and AML by mail using the mailing databases of each laboratory. This mail will include questions regarding the number of physicians active in the PCP and their names, which type of EHR currently in use and whether the physician is prepared to use an online CPOE for laboratory ordering. Physicians not responding within 2 weeks will be sent a second invitation by mail. If a physician from a PCP including more than one physician expresses interest in joining the study, the other physicians from the same practice will be invited to join. Only if all physicians in the same PCP agree to participate in the study, will they be included. If the aimed sample of 220 or 300 has not been reached after the second invitation, additional physicians will be invited by phone using the phone records of each laboratory.

Past experiences with an ongoing cluster RCT on CCDSS in primary care demonstrated that it is feasible to include at least 100 physicians by mail within a 4 week period from a sample of 1000 eligible physicians. Our sample of eligible physicians is twice as large so we foresee that the recruitment of 300 physicians should be feasible within the proposed timeframe. We will continue to invite physicians until at least 220 physicians have agreed to participate. We aim to include 300 physicians.

We will not recruit patients, but will include all patient data from those patients where laboratory test orders were made for one or more of the 17 study indications. All included patients will be followed for a period of six months, and in case their physician indicates that a potentially missed diagnosis has been made in that year, a review a of data extracted from the EHR and patient interviews will be performed to confirm the missed diagnosis.

For a subset of 250 patients with an inappropriate test, data extracted from the EHR will be reviewed to identify the downstream or cascade activities resulting from this test (see section 8.9.3 for detailed information).

8.1.1 Patient identification

We will identify eligible patients through the CPOE. All patient data will be included for those patients for which the physicians ordered laboratory tests for one of the 17 study indications. The laboratories will log all the indications for which laboratory tests were ordered, and this will allow them to identify the patients for which we will extract laboratory and patient data. A member of the research team will confirm the eligibility of the patient data for inclusion in the trial.

Patient identification will be done using the pseudonomysed national security number of the patient. All patients treated by the family physician for which the online CPOE was used to order laboratory tests will be included in the study without exclusions. Data from patients where the physicians used the paper-based order forms will not be included because the physicians do not document the indication for the laboratory tests in this situation. The pseudonomysed national security number of patient can be de-encypted allowing the study physicians to identify patients enrolled in the study while keeping the research facility blinded to their identity (see section 10 for a full description of the data collection).

8.1.2 Screening

In our study, no screening of patients for inclusion or exclusion will be necessary.

8.2 Consent

All enrolled physicians will be requested to provide a signed clinical study agreement before allocation. Participating physicians who fail or refuse to provide an informed consent will be excluded from the study.

All patients for whom a laboratory test order is made during the intervention period will be asked for consent to share their patient data with the research facility. We will use wording as in Appendix 1.1 for consent.

8.3 The randomisation scheme

PCP's will be randomized to either the intervention or control arm after stratification based on their experience in the use of a CPOE. We suspect that previous experience in using a CPOE will influence the effectiveness of order sets. Hence we will stratify all PCPs according to the self-reported experience in the use of a CPOE by its physicians. A random numbers generator will be used to randomise enrolled physicians. The research facility will be blinded to the randomization.

8.3.1 Method of implementing the allocation sequence

Randomization will be done using an electronic random numbers generator blinded to the research facility. The research facility will be kept blinded to the allocation, but collaborating laboratories will be able to identify intervention and control physicians. Allocation will be kept blinded to all study physicians until the start of the study. At the start of the study, physicians will be aware of the intervention and their allocation to either the intervention or control arm, however patients and research facility will be kept blinded to this allocation during the study and until after the data analysis.

8.4 Blinding

The research facility will be kept blinded to the allocation during the whole study until after data analysis. The collaborating laboratories will be aware of the allocation as they will need to implement the intervention. Participating physicians will be kept blinded to their allocation until the start of the study, however patients will be kept blinded.

8.5 Un-blinding

Conditions and procedures for un-blinding are not required as participating physicians will be aware of their allocation. We do not foresee any reasons (such as severe adverse events) requiring the un-blinding of the research facility. Physicians are not required to adhere to the advice of the order sets and all diagnostic decisions remain the responsibility of the ordering physician.

8.6 Baseline data

Baseline data to compare participating physicians will be obtained at the start of the study. This data includes:

- Size of the PCP (how many active physicians)
- Age of the participating physician at the start of the study
- Sex of the participating physician
- Number of active years in general practice of the participating physician at the start of the study
- Average number of tests per laboratory order in the three months prior to the study, as a measure of baseline testing volume
- Experience in the use of a CPOE prior to the study

8.7 Trial assessments

Month 0-9:

Information on the barriers and facilitators to the use of a CPOE and order sets will be obtained through interviews with participating physicians, clinical biologists and information technologists. With the GUIDES instrument (Van de Velde 2016) as guide, we will involve a purposive sample of each of these stakeholders and tailor the order sets to maximise user-friendliness and effectiveness. Differences in the implementation of the CPOE and the order sets over the laboratories will be inventoried and used to compare effectiveness. See 8.9.1 for more detail.

Month 6-9:

Information on usability of the study intervention, extracting required data, obtaining patient consent and usability of HD4DP for documenting secondary outcome measures.

Month 12:

After the intervention period of three months the following data will be provided to the research facility by the collaborating laboratories:

- For each of the 17 study indications, name and value of all tests ordered using the CPOE;
- The total volume of tests for all indications;
- The number of paper-based orders being performed alongside the CPOE and the total volume of tests this comprises.

8.8 Long term follow-up assessments

Month 9-18:

For all patients included in the trial, their physician will be requested to document all diagnoses made in his patient in the six months following the laboratory test (irrespective of possible diagnostic error). For all patients in which the physician documented a potentially missed diagnosis, a review of data extracted from the EHR will be performed by one of the researchers blinded to the allocation, to confirm that the potentially missed diagnosis is truly related to the initial laboratory test. He will document his evaluation and a second reviewers will validate his response. In case of disagreement a senior researcher will be consulted. Additionally, the patient will be interviewed by telephone to detect any additional cases of diagnostic error. A sample of patients for which no apparent diagnostic error occurred will also be interviewed by telephone to confirm the absence of diagnostic error.

Month 18-21:

For a subset of 250 patients with an inappropriate laboratory test, a review of data extracted from the EHR will be organised to identify all downstream activities. These patients will also be interviewed by telephone to identify downstream activities not recorded in the EHR. See 8.9.3 for more detail on this assessment.

Month 24:

The collaborating laboratories will provide the research facility with data on total laboratory test ordering volume for the 3 month study period. They will also provide data of the laboratory test ordering volume in the 9 months after the study period for the intervention group. These data will be used to evaluate sustainability of the intervention effects for the intervention arm.

8.9 Qualitative assessments – Nested studies

8.9.1 Implementation process evaluation

Prior to the implementation of our intervention we will research the barriers and facilitators to the use of an online CPOE and the use of order sets to guide the implementation approach. This will be assessed involving a purposive sample of various stakeholders: physicians, clinical biologists and information technologists. The GUIDES checklist (Van de Velde 2016) will be used to guide the interview and the data analysis. This checklist identifies 18 factors spread over 4 domains that influence the effectiveness of CCDSS. We will assess our intervention and the implementation of our intervention for each of these factors. The information obtained from these qualitative assessments will be used to tailor the CPOE and the order sets to maximise acceptance, usability and

effectiveness. We will report on our implementation strategy using the GUIDES checklist as backbone in a process evaluation.

8.9.2 Sustainability of implementation impact

Six months after the end of the intervention period, all participants will receive our intervention. This cross-over is motivated by two reasons: first, the laboratories perceive this intervention as a service to their customers. They cannot consent to withholding a substantial portion of their clients to this service. Moreover, prolonging the study period may demotivate participants in the control group. Second, we would like to measure the sustainability of our intervention over time in the intervention arm. The cross-over will allow us to lengthen the follow-up period for the physicians in the initial intervention arm.

8.9.3 Downstream activities

We will include one exploratory outcome in our study, this being the effect of evidence-based order sets on downstream or cascade activities. Literature suggests that improving appropriateness of laboratory testing has an effect which is much larger than simply on the amount of tests ordered. It reduces the amount of unnecessary testing due to deviant tests of unknown significance. This effect on over-diagnosis and downstream or cascade activities is often referred to as the 'Ulysses effect' (Rang 1972). Some exploratory studies have shown that the Ulysses effect may not be as important in primary care as literature suggests, but good evidence remains lacking. Evaluating these downstream or cascade effects is a resource-intensive work as this can only be done through manual review of data extracted from the EHR and completed with direct patient interviews. In a subset of 250 laboratory panels, we will review the corresponding patient charts and identify all those activities originating directly from the results of the ordered laboratory tests. We will use the methods by Houben et al (Houben 2010) as a guide to identify those laboratory panels that could potentially lead to downstream or cascade activities. We will focus on inappropriate tests in both the control and intervention arm to evaluate the extent of downstream activities and compare the difference in downstream or cascade activities between abnormal and normal results. This outcome will be measured 6 months after the initial laboratory test order. This data will also be used in any cost-effectiveness analysis resulting from this trial.

8.9.4 Physician satisfaction

There are signals that increasing eHealth initiatives are increasingly complicating daily medical practice and that this has a negative influence on physicians' professional satisfaction (Shanafelt 2016). Belgium too has known a strong increase in the use of EHRs, CPOEs and other electronic aids in health care. However, little is known on the impact of this increased electronic environment on physicians, in particular general practitioners.

In the final stages of our trial we will survey the physicians participating in the study to evaluate their satisfaction. We will design the survey during the follow-up period of the trial and send it to the participants after the final data extraction has taken place. The aim of the survey is to evaluate 2 questions:

1. How do physicians perceive the transition from a paper-based laboratory order form to an online CPOE?
2. Does the addition of evidence-based order sets facilitate the use of an online CPOE?

8.10 Withdrawal criteria

We do not foresee any withdrawal criteria for our study physicians. Study physicians are free to use or not to use the intervention. Adherence to the intervention will be a measure of implementation success. We will monitor the use of paper-based orders alongside the CPOE as an additional measure of implementation success.

8.11 Storage and analysis of samples

All data from the collaborating laboratories and all data extracted from patients through the online data extraction form or through chart review will be stored on a secured server hosted by the UZ Leuven/KU Leuven. Access to this database will be restricted to the members of the research facility to ensure the protection of patient data. This database will not include any names or detailed patient data. All data will be collected and stored using the reference number allocated to the patient and their blood sample by the collaborating laboratory.

Consent from the sectoral committee of the Federal Privacy Commission will be sought prior to the start of the study.

8.12 End of trial

Where necessary, end of trial documents and notifications will be drafted and presented.

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

Our study involves multiple levels which are not independent of each other. Lowest on the level of analysis is the individual laboratory test included in our study. We must account for the fact that these tests are not ordered entirely independent of each other in one patient, for instance, a white blood cell count is often ordered together with a white blood cell differentiation. In our analysis we will account for this level of clustering. Additionally, there is clustering on the level of the physician. When the same physician orders tests for various patients over time, each of these orders is not independent of the other. For instance, if a physician often requests chloride in patients taking diuretics, then this will probably be so in all patients taking diuretics. We must therefore also account for clustering on the level of the physician. Finally, GP's often work in primary care practices. Physicians working in the same practice tend to have similar ordering behaviour implying that the orders made by two physicians in the same practice are not independent of each other. This is the last level of clustering for which we will account. We therefore have a 4 level setting comprising test, patient, physician and primary care practice:

1. Multiple study tests per patient, assumed to be 5 per patient,
2. Multiple patients per physicians, assumed to be 42 per 3 months if there is 70% use of the online intervention,
3. Multiple physicians per primary care practice (PCP), assumed to be 2.35 based on preliminary data by Heselmans et al (Heselmans 2013).

Each of these clustering levels inflates the required sample size.

These levels are important because we will analyse at the level of the patient or the test (depending on the outcome), but we will recruit physicians and allocate primary care practices. We have calculated our sample size and translated this to the amount of physicians to be recruited and the duration of the study. For these calculations we have made several assumptions based on data from various sources (De Sutter 2007, Janssens 2014). First, we assume that the average test panel will include 5 study tests. Second, we assume that during the study period each test panel will correspond to one patient (that there will be no multiple test panels per patient). Third, we assume that each physician orders blood tests for 15 patients per week. Fourth, we assume that physicians will use the intervention in 70% of the situations (implying a 30% usage of paper-based orders) based on figures by van Wijk et al (van Wijk 2001). Fifth, we assume that a primary care practice includes 2.35 physicians, based on the recruitment data from an ongoing cluster randomized trial in primary care (Heselmans 2013).

9.1.1 Primary outcome appropriateness

To compare the effect of evidence-based order sets for 17 study indications versus control on the proportion of appropriate laboratory tests ordered by primary care physicians.

Null hypothesis: evidence-based order sets for 17 study indications have no effect on the proportion of appropriate laboratory tests ordered by primary care physicians compared to control.

Alternative hypothesis: evidence-based order sets for 17 study indications will increase the proportion of appropriate laboratory tests ordered by primary care physicians from 70% to 80% compared to control.

Figures and statistics on appropriateness of laboratory testing are grossly lacking, due to heterogeneity in the definition of appropriateness and differences in appropriateness criteria depending on the type of test. A robust figure, that seems reiterated in various studies, is that the proportion inappropriate laboratory tests is found to be around 30% (Zhi 2013, van Walraven 1998). It is believed that when using order sets in a CPOE, the appropriateness of laboratory ordering will improve. We propose that the trial should have 80% power to detect a 10% difference (in this case, from 30% to 20%) using a significance level of 5%. Appropriateness will be measured as the proportion of inappropriate study tests recorded through the CPOE. The unit of randomization is the PCP and not the patient or test, hence it is necessary to account for the lack of independence between the various tests, patients treated by the same physician and physicians working in the same PCP. In our design we account for clustering on multiple levels; clustering on the level of the individual tests ordered for the same patient, clustering for ordering patterns of the same physician for different patients and clustering for ordering patterns of physicians practicing within the same PCP. Estimates of intracluster correlation coefficients (ICCs) for process of care measures in primary care are between 0.05 and 0.15 (Campbell 1999, Campbell 2000), however estimates for ICCs regarding appropriateness of laboratory tests have been shown to vary between 0.04 and 0.288 (Littenberg 2006). To our knowledge no ICCs have been published for clustering on the various levels observed in our trial, therefore we have chosen to use a very conservative ICC estimate of 0.2 for each level of clustering in our sample size calculations, probably overestimating the design effect. Using methods proposed by Campbell (Campbell 2004) we would need 586 tests over both arms if unadjusted for clustering. We hypothesize that each panel will include approximately 5 study tests and that physicians will order laboratory tests for 42 patients per 3 months using the CPOE, assuming a 70% usage of the CPOE (van Wijk 2001). To account for clustering on the PCP level, we assume 2.35 physicians per PCP based on preliminary data from an ongoing trial (Heselmans 2013). In this situation the amount of tests would be inflated to 7305 tests, or 35 physicians in a trial lasting 3 months, taking into account multi-level clustering and attenuation of the clustering due to the amount of measures per patient (Teerenstra 2008). Figure 15 summarises the sample size calculations for the outcome appropriateness and their assumptions.

Sample size for comparison of 2 proportions (binary values): 2-sided equality

Appropriateness: pA: 70%

Clinically significant change of 10% (to pB: 80%)

$\alpha = 0.05$

$1-\beta = 0.80$

K = 1

Sample size: 586

Sample size calculations based on Campbell et al (Campbell 2004) for a trial with 80% power to detect a difference of 10% (increase op appropriateness from 70% to 80%) with a significance of 10% predict 586 tests.

Design effect of clustering on sample size based on Teerenstra et al (Teerenstra 2008):

4 level setting comprising test, patient, physician and primary care practice:

1. Multiple study tests per patient, assumed to be 5 per patient,
2. Multiple patients per physicians, assumed to be 42 per 3 months if there is 70% use of the online intervention and 1/3 indications included in the study,
3. Multiple physicians per primary care practice (PCP), assumed to be 2.35 based on preliminary data by Heselmans et al.(Heselmans 2013)

We assume an intracluster coefficient of 0.2 for each level of clustering.

Rho_n = correlation between two physicians active in the same PCP

Rho_s = correlation between two patients cared for by the same physician

Rho_e = correlation between two tests ordered for the same patient

n_n = mean amount of physicians per PCP

n_s = mean amount of patients per physician

n_e = mean amount of study tests per patient

$Phi_e = 1+Rho_e*(n_e-1)$

$Phi_s = 1+Rho_s*(n_s-1)*w_e$

$Phi_n = 1+Rho_n*(n_n-1)*w_n$

$w_e = (n_e*Rho_e)/(1+Rho_e*(n_e-1))$

$w_s = (n_s*Rho_s)/(1+Rho_s*(n_s-1))$

The final design effect (DE) = $Phi_e*Phi_s*Phi_n$

Applied to our protocol:

n_n = mean amount of physicians per PCP = 2.35

n_s = mean amount of patients per physician = 42 per 3 months

n_e = mean amount of study tests per patient = 5

$Phi_e = 1+Rho_e*(n_e-1) = 1.8$

$Phi_s = 1+Rho_s*(n_s-1)*w_e = 5.56$

$Phi_n = 1+Rho_n*(n_n-1)*w_s = 1.25$

$w_e = (n_e*Rho_e)/(1+Rho_e*(n_e-1)) = 0.56$

$w_s = (n_s*Rho_s)/(1+Rho_s*(n_s-1)) = 0.913$

The final design effect (DE) = $Phi_e*Phi_s*Phi_n = 1.8*5.56*1.25 = 12.465$

586 test * 12.465 (DE) = 7305 test = 1460 patients = **35 physicians during 3 months**

Figure 15: Sample size calculations for primary outcome appropriateness including inflation due to multi-level clustering

9.1.2 Secondary outcome 'missed or delayed diagnoses'

To demonstrate non-inferiority in the effect of evidence-based order sets for 17 study indications versus control on the incidence of missed or delayed diagnoses by primary care physicians.

Null hypothesis: evidence-based order sets for 17 study indications increase the incidence of missed or delayed diagnosis in primary care by more than 1%.

Alternative hypothesis: evidence-based order sets for 17 study indications do not worsen the incidence of missed or delayed diagnoses by primary care physicians compared to control, i.e. pA – pB < 1%, with pA and pB being the proportion of missed diagnoses in the intervention and control groups, respectively.

To our knowledge there are no sound statistics on the percentage missed diagnoses due to laboratory testing in primary care. Panesar et al (Panesar 2016) estimated that two to three per hundred consultations in primary care result in safety incidents. Between 4 and 45% of these safety incidents may be related to misdiagnosis or missed diagnoses. Assuming 2.5% missed diagnoses in primary care, we calculated that the trial, with an 80% power to detect a non-inferiority of a 1% difference using a significance level of 5%, would need 6032 patients in total. Previous studies have illustrated that in primary care ICCs for clinical outcomes are lower than those for process outcomes and the ICC for adverse effects to be around 0.025 (Adams 2004). Although this may not seem correct, the chances that a physician consistently misses the same diagnosis is less probable than consistently ordering the same test for the same indication. A missed or delayed diagnosis will more probably lead to a change in practice than over- or underutilization of a laboratory test. For this outcome, the unit of analysis will be individual patients and not individual tests as for appropriateness. Therefore, there is one level of clustering less to account for. Assuming a 3 month period in which laboratory tests are ordered for 42 patients, we would need to recruit 290 physicians. In the case of a 6 month period, implying 84 patients for which a laboratory panel is requested, we would need to recruit 220 physicians. For this clinical outcome we will not account for clustering on the level of the PCP as there is no evidence that this influences the amount missed diagnoses by individual physicians. Intuitively, there is no reason to assume that two physicians working together in the same practice would have a greater probability of missing the same diagnosis. Because we believe this outcome to be important in convincing physicians in the widespread use of order sets for laboratory tests, we have chosen to power our study to include this outcome. Figure 16 summarises all the sample size calculations for the outcome 'missed or delayed diagnoses' and their assumptions.

Sample size for comparison of 2 proportions (binary values): non-inferiority trial
Missed diagnoses: pA: 2.5%
Missed diagnoses: pA: 2.5%
Clinically significant change of 1%
$\alpha = 0.05$
$1-\beta = 0.80$
$K = 1$
Sample size: 6032
Sealed Envelope Ltd. 2012. Power calculator for binary outcome non-inferiority trial. [Online] Available from: https://www.sealedenvelope.com/power/binary-noninferior/ [Accessed Wed Jul 20 2016].
$DE = 1 + \rho(n-1)$
n = number individuals per cluster
ρ = intracluster correlation coefficient
We account only for the clustering on the level of the physician.
n = 42 for a trial lasting 3 months
n = 84 for a trial lasting 6 months
$\rho = 0.025$
for a trial lasting **3 months**: DE = 2.025 which implies **290 physicians (≈300 physicians)**
for a trial lasting **6 months**: DE = 3.075 which implies **220 physicians**

Figure 16: Sample size calculations for secondary outcomes missed or delayed diagnoses including inflation due to clustering

9.1.3 Final sample size

The trial will have sufficient power for both the primary and secondary outcome. Hence, a total of 300 physicians will be included.

Therefore the trial will be overpowered for the primary endpoint and be able to detect much smaller differences between the two groups than the predefined difference of 10% that was set out to be found. Therefore, assuming a sample of 300 recruited physicians, the minimal difference that can be found with a statistical power of 90% using a significance level of 5%, based on the assumptions described in section 9.1, was calculated. With 300 recruited physicians, it is expected that the trial will include 12600 patients and a total of 63000 tests. Removing the design effect (by dividing by 12.465), this corresponds with a a total of 5054 'independent' tests and provides the trial with a 90% power to detect a difference as small as 4.1%.

9.2 Planned recruitment rate

We plan to recruit physicians through the collaborating laboratories. We have no data on the rate with which we can expect to recruit the required amount of physicians. In an ongoing trial on decision support in primary care the required amount of 120 physicians out of 1000 eligible physicians was accomplished within 4 weeks of the first invitation. The amount of eligible physicians in our trial is around 2000, suggesting that it should be feasible to recruit 300 physicians within 2 weeks of the first invitation.

We have estimated that each study physician orders 15 laboratory panels per week for the 17 conditions or indications included in our study. This is a conservative estimate ensuring that we will be able to analyse sufficient data after the 3 month period. For the outcome of appropriateness we need to analyse at least 7305 tests (for a three month period, this would be the amount of tests ordered by 35 physicians). We need these three months to expose at least 12 600 patients (42 patients x 300 physicians) to our intervention for whom we will collect data on missed diagnoses. In case the rate of patient exposure were to be slower than expected, we will prolong the intervention period to include at least 12 600 patients.

9.3 Statistical analysis plan

Full details of the statistical analysis will be described in a Statistical Analysis Plan which will be finalised prior to database lock.

9.3.1 Summary of baseline data and flow of patients

For the comparison of PCP characteristics, continuous data will be presented by their average and standard deviation or median and interquartile range and comparisons between the allocated groups will be done using a t-test or Wilcoxon or rank-sum test, as appropriate)

For comparisons of physician characteristics, comparisons will be made using generalised estimating equations (GEE), using PCP as the clustering variable. An independent working correlation matrix will be used to account for correlations with the clusters. For continuous variables, an identity link and normal distribution will be used; for binary variables, a logit link and binary distribution; for categorical variables, a cumulative logit link and multinomial distribution. Means and proportions per group will be estimated from the model.

For the comparison of patient characteristics, similar methodology will be used as for physician characteristics, but using physician as the clustering variable.

9.3.2 Primary outcome analysis

To assess differences between the allocated groups in the proportion appropriate tests, a logistic GEE model will be used: of interest are the marginal proportions, not the individual probabilities of test to be appropriate.

The logistic GEE model will include the allocated group as a factor and patients as the clustering variable. The effect of the intervention will be expressed as the difference in proportions and will be presented together with its associated 95% confidence interval. The proportion of appropriate tests in the two allocated groups will also be estimated from the GEE model and presented with their 95% confidence intervals.

Appropriateness for the composite of all study tests will be compared between intervention and control groups groups. Furthermore, an analysis will be performed that only includes patients who have no indications in addition to the 17 study indications. This additional analysis will correct for an overestimation of inappropriate tests when more than one indication is selected, including indications not under evaluation. These tests would be considered inappropriate even though they could be appropriate according to one of the other indications not being evaluated.

The analyses will be performed on all patients from all physicians according to their allocated group.

9.3.3 Secondary outcome analysis

9.3.3.1 Missed diagnoses

The proportion of patients with a missed diagnosis will be analysed by means of a logistic GEE model that includes a factor for allocated group and uses PCP as the clustering variable. An independent working correlation matrix will be used. The proportion of patients with a missed diagnosis and associated 95% confidence intervals will be estimated from the model.

The difference in proportions will be obtained by subtracting the two proportion. The associated standard error will be calculated from the rules for the variance of a difference between two independent estimates. The 95% confidence interval for the difference will be calculated.

The non-inferiority limit for missed diagnoses is 1%, i.e. the intervention will be deemed non-inferior if the difference between the allocated groups (intervention – control) is less than 1%. Therefore, the intervention will be deemed non-inferior if the upper limit of the 95% confidence interval lies below 1.

As for the primary endpoint, the analysis will be performed for all 17 study indications together. An analysis will be performed that only includes patients who have no indications in addition to the 17 study indications

9.3.3.2 *Test volume*

The total number of tests will be analysed using a Poisson GEE model that includes allocated group as factor in the model and physician as clustering variable. No offset will be used. The number of tests per patient for each group will be estimated from the model and presented together with their associated 95% confidence intervals. The effect of the intervention will be presented as the ratio between the two numbers with its 95% confidence interval. Statistical significance will be assessed at a significance level of 5%.

9.3.4 *Exploratory outcome analysis*

9.3.4.1 *Downstream or cascade activities*

The total number of cascades per patient will be analysed using the same methodology as for the total number of tests (see section 9.3.3.2).

9.4 Subgroup analyses

Subgroup analyses per indication will be done for the primary outcome and for the proportion of patients with missed diagnosis. In addition, an analysis will be performed that only includes patients who have no indications in addition to the 17 study indications.

9.5 Adjusted analysis

For the primary endpoint and the missed diagnoses, the following adjusted analyses will be performed:

- Volume of physician practice, i.e. the total number of tests prescribed the previous year.
- Total number of patients in practice
- Physician's age or years worked.

9.6 Interim analysis and criteria for the premature termination of the trial

The intervention period will last 6 months, with a first data collection after 3 months, and there is little or no risk of adverse effects. We do not foresee an interim analysis and any criteria for premature termination of the trial. In case a physicians is prompted to order a series of tests he does not agree with, then he is free to order other or additional tests. This range of freedom should avoid potentially hazardous situations in the improbable situation that this should arise.

9.7 Subject population

We will include all data for test orders ordered through the CPOE. Tests ordered through paper-based order forms will not be included in the analysis as these orders were not subject to the intervention. Of the paper-based orders, a significant amount will be orders made during house calls or situations in which a computerized order entry is not feasible. Additionally, orders through a paper-based order form lack information on the indication for the tests making it impossible to assess whether these tests are (in)appropriate. We will monitor the number of paper-based orders as a measure of implementation success of the CPOE.

9.8 Procedure(s) to account for missing or spurious data

Crucial in our study is the reporting of study physicians on both the outcome appropriateness and the outcome missed or delayed diagnosis. We have foreseen two interventions to prevent physicians from failing to document the indications for which he is ordering laboratory test.

1. During the trial period, physicians will not be able to validate a laboratory order without entering one or more indications. Physicians attempting to enter laboratory tests through the

CPOE will be prompted to enter at least one indication before being able to validate the order. This prompt will be deactivated after the intervention period.

2. We foresee a financial incentive for study physicians which will be granted at two intervals: a first part at the end of the data collection for appropriateness, and a second part at the end of the data collection for missed diagnoses through the electronic data collection form. This financial incentive will aid in maximizing data reporting by study physicians and is a strategy for preventing missing data.

With these interventions we believe we will not have to deal with any missing or spurious data and do not foresee any procedures to account for these.

9.9 Other statistical considerations.

As mentioned in 9.3.1, restricting our evaluation to the 17 study indications may overestimate the amount of inappropriate tests when multiple indications are documented including an indication not under evaluation. These tests, even though possibly appropriate for the additional indication will be considered inappropriate for the study indication. The subgroup analysis of appropriate tests for those orders containing only study indications will allow us to correct for this overestimation.

9.10 Economic evaluation (optional)

If our trial can show effectiveness, we aim to perform an economic evaluation of our intervention. The aim of this evaluation is to assess the value-for-money offered by using order sets for appropriate laboratory tests.

We would include all direct healthcare costs of performing tests, indirect costs of the intervention and make an assessment of the downstream productivity gains and cost-savings that occur through improved (or more efficient) testing. All costs would be assessed from both a healthcare payer and a societal perspective, distinguishing as much as possible between various cost-sharers in the specific Belgian context.

These estimates would be compared to various effect measures in order to assess the cost-effectiveness of implementing order sets. A first starting point would be to calculate the cost per appropriate laboratory test in both arms of the trial. This should provide a direct estimate of the efficiency gains achievable through this intervention.

In addition to these efficiency assessments of improved testing we would also investigate the distributional aspects of this measure. We would map patients' socio-economic background and explore:

1. how use of testing is distributed over socio-economic strata in Belgium, and
2. whether use of order sets has an equity impact.

Assessing socio-economic background can be done by contacting patients via surveys, asking physicians to make an assessment of the patients' status (income and overall health) and by assessing whether the physician's practice is located in a relatively deprived area or not.

10 DATA HANDLING

10.1 Data collection tools and source document identification

Data collection will be performed through the Healthdata.be tool developed and maintained by the Scientific Institute for Public Health (WIV-ISP). This tool allows for secure, encrypted and pseudonomysed data transfer from multiple sources into a central data warehouse. Data from a single patient can be collected through this system from more than one source while still ensuring anonymity. The healthdata.be platform uses two software tools to capture and collect data. The HD4DP (health data for data providers) tool captures the data from within the EHR or LIS and allows the data provider to complement the tool with additional data which is not stored in the EHR in a structured format. The source data remains in the database of the data provider and only an excerpt of this source data is transferred to the research facility. Data can be collected continuously or in a one-time fashion depending on the resource. All data is transferred through encrypted channels, using highly secured national ehealth encryption algorithms, to the research facility that can view the

data using the HD4RES (health data for researchers) tool. Figure 17 illustrates the data flows from the data provider to the research facility.

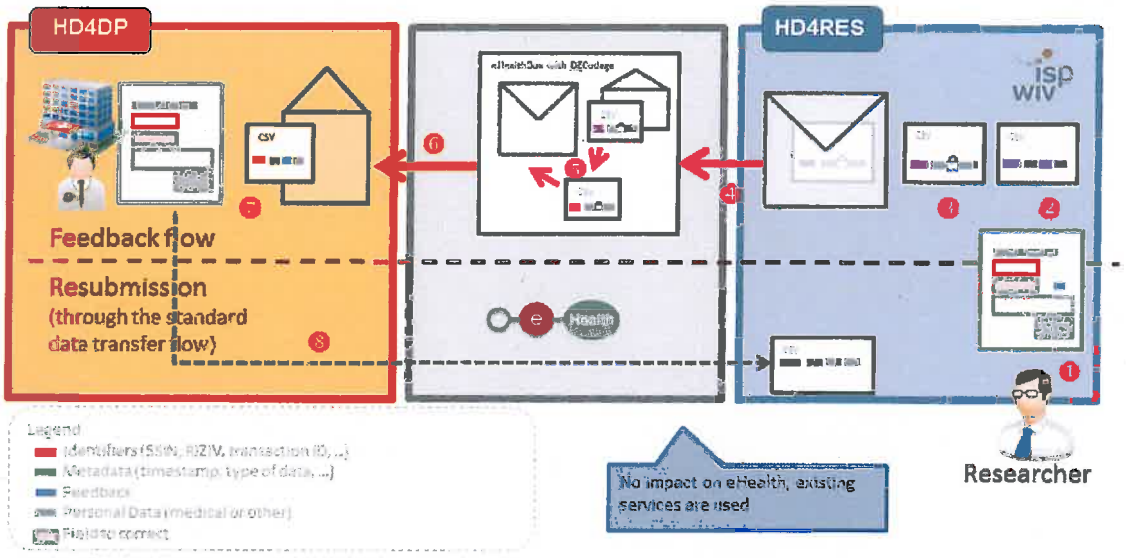

Figure 17: Data flows using the Healthdata.be project. From http://www.healthdata.be (02/05/2017).

Data will be collected from 4 sources: the LIS, the primary care EHRs, directly from the primary care physicians and directly from the patients. Before import into the data warehouse, all data is validated in the 'landing zone' and if required sent back to the data provider for additional information. Each of these data flows will be defined, including a full description of each data element. All these data will be pseudonomysed to allow integration of data from a single patient from multiple sources. The identity of the individual patient will be blinded to the research facility at all times. Figure 18 illustrates these data flows. For a full and detailed description of this process we refer to the deliberation of the Sector Committee for Social Security and Health of the Privacy Commission of May 16, 2017 (CBPL 2017).

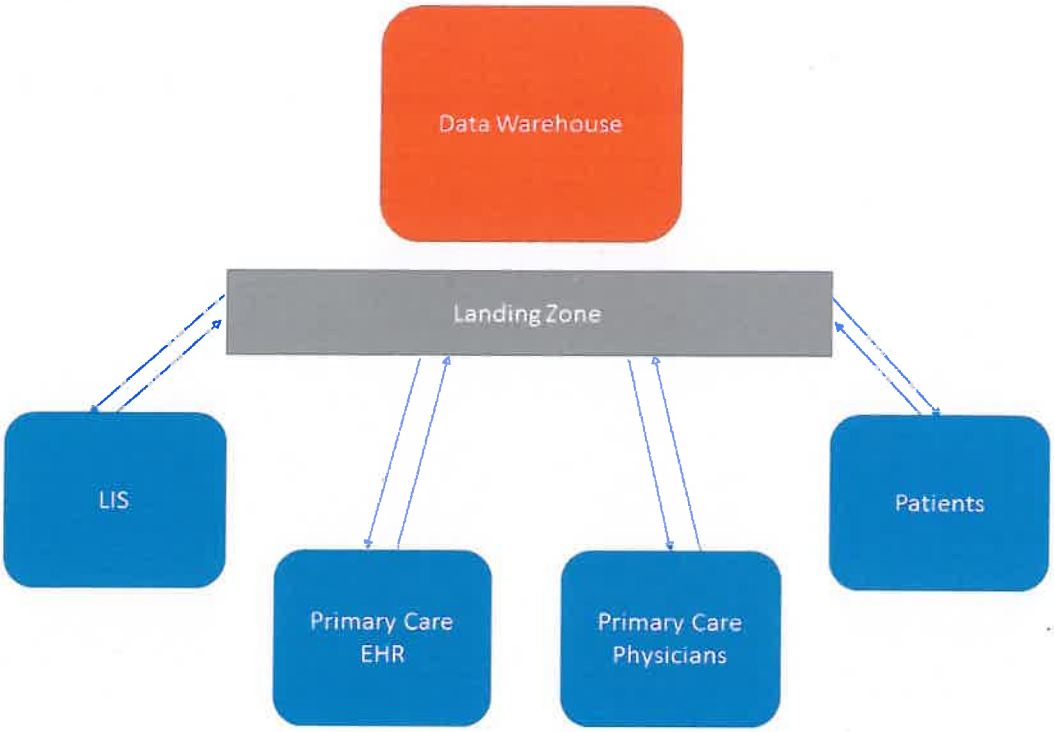

Figure 18: Data flows from 4 sources (LIS, primary care EHR, directly from primary care physicians, and directly from patients). Data from these sources is validated (in the landing zone) before it is integrated into the data warehouse. Figure adapted from www.healthdata.be.

Data will be collected and recorded through the LIS of collaborating laboratories or the EHR of study physicians. The collection and processing of data (from patients enrolled in this study) will be limited to those data that are necessary to fulfil the objectives of the study. These data will be collected using secure national ehealth communication tools and processed with the necessary precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be guaranteed by the WIV-ISP, who will be responsible for data storage. Personnel whose responsibilities require access to personal data agree to keep the data confidential.

Data collection is the responsibility of the research facility under the supervision of the investigator. The investigator will maintain complete and accurate documentation for the study. All source documents will be reviewed by the clinical team to ensure that they are accurate and complete.

As defined in section 1.52 of the ICH Guideline for Good Clinical Practice (ICH E6) source documents may include: original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes....)

10.2 Data handling and record keeping

The Scientific Institute for Public Health will maintain the data warehouse, including all eCRFs. The data warehouse is highly secured and access to the database is only possible through an extranet connection which does not allow full access to the data. Only a small number of members of the Scientific Institute for public Health are authorized to access the full data. All access to the data warehouse is tracked through IBM InfoSphere Guardium®.

All data transfer is organised through the highly secured national ehealth channels. These information channels provide end-to-end encryption using the personal certificates of each of the

participating physicians. The ehealth platform will also be responsible for the pseudonymisation of patient data as Trusted Third Party. The Scientific Institute for Public Health will have no knowledge of the identity of the patient in any way.

The healthdata.be platform has dedicated a party responsible for data security

10.3 Access to Data

Access to the trial data is guaranteed through the extranet environment of the healthdata.be platform. Only authorized researchers or monitors will be granted access to the data warehouse. All activity is monitored in real-time by IBM InfoSphere Guardium®, which logs identity of the users, time and duration of activity, and results of the activity.

10.4 Archiving

The Sponsor is responsible for archiving study specific documentation (such as but not limited to protocol, potential amendments and final report) for at least twenty years. The database of patient data will be stored in a register at the Scientific Institute for Public Health. Destruction of essential documents will require authorization from the Sponsor.

11 MONITORING, AUDIT & INSPECTION

Due to the nature of the collected data (direct import of pseudonymised from data providers), no data monitoring of source documents is possible. Access to the trial database will be granted for monitoring or auditing purposes where deemed necessary.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Research Ethics Committee (REC) review & reports

The study will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. Before the start of the study, this protocol, the informed consent forms and other related documents e.g. advertisements and GP information letters, will be submitted for review to the REC and to the Sector Committee for Social Security and Health of the Privacy Commission. The study shall not commence until such approvals have been obtained.

Any subsequent protocol amendments will be submitted to the REC and Sector Committee for approval. No substantial amendment that require review by REC will be implemented until the REC grants a favourable opinion for the study.

The study can and will be conducted only on the basis of prior informed consent by the study participants, or their legal representatives, to participate in the study. Extensive discussion of risks and possible benefits of participation will be provided to the patients and/or their families. The participating physician shall obtain a signed informed consent form for all study participants prior to their enrolment and participation in the study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The research facility shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

All correspondence with the REC shall be retained in the Trial Master File/Investigator Site File.

The Chief Investigator acknowledges that it is his responsibility to produce annual progress reports (APR) and he will do so by submitting to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

The Chief Investigator shall notify the REC of the end of the study. Should the study be ended prematurely, the Chief Investigator will notify the REC and include the reasons for the premature termination. The Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

12.2 Peer review

Peer review will be conducted by expert referees to the professional and scientific standards expected for clinical studies

12.3 Public and Patient Involvement

The order sets implemented within the CPOE of the participating laboratories will be made publicly available through the website www.ebmpracticenet.be, a platform open to all Belgian citizens and funded by RIZIV-INAMI. Patient versions will be made available in Dutch through the platform www.gezondheidenwetenschap.be, which is publicly available and funded by the Flemish Governement.

The development of the intervention will be done together with information technologists responsible for the development of E-Lab and LabOnline. LabOnline, developed by Moonchase, has been or is being implemented in various laboratories including LBS (Brussels), Laboratory Declerck (West Flanders), Laboratory Van Waes (Bruges), Iliano (Ghent), CRI (Ghent) and AKL (Lier). The potential for a wider implementation with the identical intervention is great.

EBM*Practice*Net is an active participant in the eHealth criteria for meaningful use by primary care physicians. Monitoring the use of order sets could be used as a criterion in the meaningful use criteria for all primary care physicians.

12.4 Regulatory Compliance

Before the start of the study, this protocol and other related documents will be submitted for review to the Sector Committee for Social Security and Health of the Privacy Commission. The study shall not commence until such approvals have been obtained.

This study protocol and the conduct of the study in general is in compliance with applicable law, including but not limited to the Belgian law of May 7th 2004 regarding experiments on the human person and any relevant amendments.

12.5 Protocol compliance

The Chief Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

It is acknowledged and agreed that prospective, planned deviations or waivers to the protocol are not allowed under applicable regulations on clinical studies and must not be used. However, should there be an accidental protocol deviation, such deviation shall be adequately documented on the source documents and on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Protocol deviations which are found to frequently recur, will require immediate action. Chief Investigator acknowledges that such recurring protocol breaches could be potentially classified as a serious violation (as defined under section 12.6).

12.6 Notification of Serious Breaches to GCP and/or the protocol

It is understood that "a serious violation" is likely to effect to a significant degree

- the safety or physical or mental integrity of the participants of the study; or

- the scientific value of the study

The Sponsor shall be notified immediately upon becoming aware of a serious violation during the study conduct phase. The Sponsor shall notify the licensing authority in writing of any serious violation of the conditions and principles of GCP in connection with that study; or the protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that violation.

12.7 Data protection and patient confidentiality

The study will be conducted in compliance with the requirements of the Belgian Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and the European Data Protection Act. Any collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with the aforementioned personal data protection laws.

Any personal data shall be treated as confidential at all times including during collection, handling and use, and that the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with data protection legislation. The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

The personal data of study participants will be encoded, which means that they can only be related to an identifiable person by means of a unique code. The unique code will only be in the possession of the members of the study team who are in direct contact with the study participants. In no event will the coded personal data include personal identifiers, including any Study participant's initials. Such coded personal data can only be traced or linked back by said study team members, and said study team members shall treat these codes as strictly confidential.

Only anonymized personal data will be disclosed to KCE or, where specifically requested by KCE, coded personal data. In no event shall any of the reports, documents, information disclosed to KCE include data that may be linked to the specific identity of a study participant. The Sponsor shall make sure that the key to personal identities of all persons to whom the data relates is kept in a separate and secure place in compliance with applicable data privacy legislation and shall not be disclosed to KCE or unauthorized persons.

All study related data and documents will be stored for twenty (20) years, in accordance with Belgian legislation.

12.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator hereby declares having no financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; not having received any significant payments of other sorts from the Sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, honoraria, ownership interest that may be related to products, services or interventions considered for use in the study, or that may be significantly affected by the study; having no commercial ties with any pharmaceutical, behaviour modification, and/or technology company; nor having any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

In consideration of participation in the study, the nominated payee will receive the sums set out in the payment schedule attached to the clinical trial agreement.

12.9 Indemnity

The Sponsor has foreseen an insurance policy for this trial as set out in the Law of 2004 through Amlin Europe NV, in collaboration with Vanbreda Risks & Benefits NV, with contract number 299.053.700. The Sponsor shall throughout the duration of the study effect and maintain this insurance policy providing an adequate level of cover in respect of all risks which may be incurred by the Sponsor arising out of the Sponsor's performance of the study.

The terms or the amount of cover of any insurance shall not relieve the Sponsor of any liabilities under the clinical trial agreement.

12.10 Amendments

In accordance with the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor may make a non-substantial amendment at any time during a study. If the Sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the Sponsor must submit a valid notice of amendment to the licencing authority for consideration. If the Sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 28 days of receipt of the notice. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

12.11 Access to the final trial dataset

The study results will be owned by the party who generates them. The Sponsor will have access to the study data. At the end of the study, KCE will receive from Sponsor specific study data. This will only be anonymous study data or, where requested by KCE, coded personal data are made available to KCE.

The study data shall not be provided to a third party without the prior written approval of KCE, which approval KCE shall not unreasonably withhold or delay and which KCE may subject to specific conditions in order to ensure that the provision of said study data does not have a negative impact on the further performance of the study, the rights granted to KCE under the research agreement and/or the benefit of the Study for the patients and/or the public payers.

13 DISSEMINATION POLICY

13.1 Dissemination policy

The results of the study shall be owned by the party who generates them.

The results of the study owned by Sponsor and/or (where applicable) any collaborator shall be disseminated as soon as possible, by disclosing them to the public by appropriate means, including in scientific publications (in any medium). Sponsor shall inform and discuss its dissemination strategy with KCE in advance.

The final Study report should be made available for review by KCE before the results are disseminated. KCE shall be notified prior to any dissemination (including publication) (whether in oral, written or other form) of the foreground IP or results or study data or of matters arising from the study. The Chief Investigator shall send one draft copy of the proposed dissemination to KCE at least ten (10) days for an abstract and thirty (30) days for a manuscript before the date intended for dissemination. For the avoidance of doubt, this obligation continues after the end of the study. KCE may object within thirty (30) days of receiving notification, if, in its reasonable opinion, the dissemination (or the timing thereof) is not in the public interests. In the event Chief Investigator or (where applicable) any collaborator intends not to protect the results of the study it needs to formally notify KCE thereof before the dissemination takes place, Sponsor shall ensure that any dissemination is scientifically correct, objective and unbiased (taking into consideration the primary endpoint(s)).

In the event of a multicentre study, Sponsor nor its collaborators shall independently publish or otherwise disclose any findings resulting from the study before publication of the main multicentre publication.

Any dissemination shall acknowledge KCE's financial support and carry a disclaimer as KCE may require in accordance with the clinical trial agreement.

Open access will be ensured (free of charge, online access for any user) to all peer-reviewed scientific publications relating to the results of the study owned by it and/or the collaborators. In particular, Sponsor shall: (i) As soon as possible and at the latest on publication, deposit a machine readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications; moreover Sponsor must aim to deposit at the same time the research data needed to validate the results of the study presented in the deposited scientific publications; and; (ii) Ensure open access to the deposited publication, via the repository at the latest on publication (if an electronic version is available for free via the publisher) or, within six (6) months of publication in any other case.

13.2 Authorship eligibility guidelines and any intended use of professional writers

All reports will be written by researches directly involved in the study and supervised by the Steering Committee. Only researchers or participants actively involved in parts of the study will be eligible for authorship.

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APPENDICES

APPENDIX 1. STUDY MANAGEMENT

Appendix 1.1. Patient informed consent

The elements in this ICF are based on the UZ Leuven model for observational studies. Certain elements may still change depending on EC advice.

I Necessary information for your decision to participate

Introduction

You are being invited to take part in a comparative clinical study. With this study we want to investigate the influence a computerized system, designed to avoid unnecessary laboratory tests, on the laboratory test orders by physicians. This means that the laboratory test order you have been offered was either prescribed in the usual manner, in accordance with the conditions of good medical practice or through this computerized system. This systems is designed to improve care, however this does not mean that physicians not using this intervention offer bad care.

We are simply asking you whether we can collect data from your medical records to be able to combine them with those of other patients receiving the same treatment and to process them statistically for research purposes.

Apart from a few questionnaires we may ask you to complete, no additional diagnostic or monitoring procedure will be proposed.

Before you agree to take part in this study, we invite you to take note of its implications in terms of organisation, possible risks and benefits, to allow you to make a decision with full awareness of the implications. This is known as giving "informed consent".

Please read these few pages of information carefully and ask any questions you want to the investigator or his/her representative.

There are 3 parts to this document: the information essential to your decision, your written consent and supplementary information (appendices) detailing certain aspects of the basic information.

If you take part in this study, you should be aware that:

- The treatment offered to you by the investigator in accordance with current recommendations will not be altered if you take part in the study.
- This clinical study is being conducted after having been reviewed by an ethics committees.
- Your participation is voluntary and must remain free from any coercion. It requires the signature of a document expressing your consent. Even after having signed this document, you can stop taking part by informing the investigator.
- The data collected on this occasion are confidential and your anonymity is guaranteed during publication of the results.
- Insurance has been taken out in case you should suffer any damage in connection with your participation in this clinical study.
- You may contact the investigator or a member of his/her team at any time should you need any additional information.

Further information about your "Rights as a participant in a clinical study" can be found in appendix XX.

Objectives and course of the study

This clinical study has been organised to study the effects of a computerized system on the laboratory test ordering by general physicians.

We are inviting you to take part in this clinical study because your doctor has ordered laboratory tests for you within the context of your clinical situation.

This clinical study is to include around 300 general practitioners (GPs) and 12 600 patients in Belgium.

Your participation in the study will last around 9 months, during which we will ask your doctor to send us information related to your treatment, to the progression of your clinical situation, the results of the ordered laboratory tests, and the results of additional tests which may have been ordered.

It is possible that you will be contacted by an independent researcher to complete a telephone questionnaire. In this case, a report form will be generated by the software system in which your identity will be made known to the independent researcher who will be taking the interview. Once all the data has been entered in to the report form, they will be coded. The research facility will not know your identity at any moment.

Description of risks and benefits

As indicated above, neither the treatment that has been proposed or the diagnostic and monitoring procedures for your clinical situation go beyond good medical practice. No risk, in terms of health, can be linked to your participation in this study.

Similarly, you should not expect any personal benefits as a result of taking part in the study. Know only that your participation will allow us to better understand the influence of a clinical decision support service on the laboratory orders by your physician and thus to offer better treatments in the future.

Withdrawal of consent

Your participation is voluntary and you are entitled to withdraw your consent to take part in the study for any reason, without having to justify your decision.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point at which you withdraw will be retained. No new data may be sent to the sponsor.

If you take part in this study, we ask you:

- To cooperate fully in the smooth running of this study.
- Not to conceal anything such as information relating to your state of health, the medication you are taking or the symptoms you are experiencing.
- To inform your doctor if you are asked to take part in another study to discuss with him/her the possibility of taking part in this study and to see whether you should then stop taking part in the present study.
- To accept the possible need for investigator/GP contact for the gathering of additional information if appropriate

Contact

If you need further information, but also if you have problems or concerns, you can contact the investigator (Delvaux Nicolas) or a member of his/her research team (De Burghgrave Tine) on the following telephone number (016/37 72 76).

If you have any questions relating to your rights as a participant in a clinical study, you can contact the patient rights ombudsman[a] of UZ / KU Leuven.

II Informed consent

Participant

I declare that I have been informed of the nature of the study, its purpose, its duration, the possible side effects and what is expected of me. I have taken note of the information document and the appendices to this document.

I have had sufficient time to think about it and discuss it with a person of my choice (GP, relative).

I have had the opportunity to ask any questions that came to mind and have obtained a favourable response to my questions.

I understand that data about me will be collected throughout my participation in this study and that the investigator and the sponsor of the study will guarantee the confidentiality of these data.

I agree to my personal data being processed as described in the section dealing with confidentiality guarantees (page x/y). I also consent to these data being transferred to and processed in countries other than Belgium.

I agree to the research data collected for the purposes of this study being processed at a later date provided this processing is limited to the context of the present study (better understanding of the disease and its treatment).

I agree to my GP or other specialists in charge of my health being contacted if required to obtain additional information about my health.

I have received a copy of the information to the participant and the informed consent form.

Surname, first name, date and signature of the volunteer.

Witness/Interpreter

I was present during the entire process of informing the patient and I confirm that the information on the objectives and procedures of the study was adequately provided, that the participant (or his/her legal representative) apparently understood the study and that consent to participate in the study was freely given.

Surname, first name and qualification of the witness/interpreter:

Date and signature of the witness/interpreter.

Collaborating GP

I, the undersigned, [surname, first name] GP, confirm that I have verbally provided the necessary information about the study and have given the participant a copy of the information document.

I confirm that no pressure was applied to persuade the patient to agree to take part in the study and that I am willing to answer any additional questions if required.

I confirm that I operate in accordance with the ethical principles set out in the latest version of the "Helsinki Declaration", the "Good Clinical Practices" and the Belgian Law of 7 May 2004 related to experiments on humans.

Surname, first name, date and signature of the investigator's representative	Surname, first name, date and signature of the investigator

III Supplementary information

Supplementary information on the organisation of the study

The study will not require any additional contacts with investigators. All the data will be collected through your GP, your medical record and the laboratory. It is possible that you will be contacted by phone at the end of the trial about 1 year from now. This research assistant will conduct a telephone interview on your current medical situation and any additional investigations that were performed after the laboratory test that was taken today. Finally, it is possible that additional coded information will be requested from other institutions such as RIZIV-INAMI or the Intermutualistisch College regarding care you received and its cost.

Supplementary information on the protection and rights of the participant in a clinical study

Ethics Committee

This study has been reviewed by the ethics committee of UZ / KU Leuven, which has issued a favourable opinion. It is the task of the Ethics Committees to protect people who take part in a clinical trial. They make sure that your rights as a patient and as a participant in a clinical study are respected, that based on current knowledge, the study is scientifically relevant and ethical.

You should not under any circumstances take the favourable opinion of the ethics committee as an incentive to take part in this study.

Voluntary participation

Before signing, do not hesitate to ask any questions you feel are appropriate. Take the time to discuss matters with a trusted person if you so wish.

Your participation in the study is voluntary and must remain free of any coercion: this means that you have the right not to take part in the study or to withdraw without giving a reason, even if you previously agreed to take part. Your decision will not affect your relationship with the investigator or the quality of your future therapeutic care.

If you agree to take part in this study, you will sign the informed consent form. The investigator will also sign this form to confirm that he/she has provided you with the necessary information about the study. You will receive a copy of the form.

Costs associated with your participation

The sponsor has arranged to compensate the hospital for the time devoted to the study by the investigator and his/her team. You will not receive any compensation for your participation in this study. Furthermore, the study will not involve any additional costs for you.

Guarantee of confidentiality

Your participation in the study means that you agree to the investigator collecting data about you and to the study sponsor using these data for research purposes and in connection with scientific and medical publications.

You are entitled to ask the research facility what data are being collected about you and what is their use in connection with the study. This data concerns your current clinical situation but also some of your background, the results of examinations carried out within the context of care of your health in accordance with current standards. You have the right to inspect these data and correct them if they are incorrect[b].

b These rights are guaranteed by the Law of 8 December 1992 on the protection of privacy in relation to the processing of personal data and by the Law of 22 August 2002 on patient rights.

This means that he/she undertakes not only never to reveal your name in the context of a publication or conference but also that he/she will encode your data before sending them to the manager of the database of collected data. The Scientific Institute for Public Health (WIV-ISP) is responsible for guaranteeing the safety and security of your data. When sending your medical data to the WIV-ISP, your identity is anonymised using a complicated encryption. Your identity can be made known again if additional information is necessary, but the research team will never know your name. If you are contacted by phone for additional information, this will be done by an independent person who is bound by professional secrecy and who will have no further access to your medical data after the interview.

Your GP will be the only one to be able to establish a link between the data transmitted throughout the study and your medical records[c].

The personal data transmitted will not contain any combination of elements that might despite everything allow you to be identified[d].

For the study data manager designated by the sponsor, the data transmitted will not allow you to be identified. The latter is responsible for collecting the data gathered by all investigators taking part in the study, processing them and protecting them in accordance with the requirements of the Belgian law on the protection of privacy.

To verify the quality of the study, it is possible that your medical records will be examined by third parties (ethics committee, representatives of the study sponsor, external auditors). In any event, this may only take place under the responsibility of the investigator or of one of his/her colleagues and by persons subject to the obligation of professional secrecy.

These (encoded) data will be able to be sent to Belgian or other regulatory authorities, to the relevant ethics committees, to other doctors and/or to organisations working in collaboration with the sponsor.

They will also be able to be sent to other sites of the sponsor in Belgium and in other countries where the standards in terms of the protection of personal data may be different or less stringent[e].

Your consent to take part in this study therefore also implies your consent to the use of your encoded medical data for the purposes described in this information form and to their transmission to the aforementioned people and authorities.

The sponsor undertakes only to use the data collected within the context of the study in which you are taking part.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point at which you withdraw will be retained. No new data may be sent to the sponsor.

Insurance

In an observational study, the only possible risk would be a flaw in the measures taken to protect the confidentiality of the private information about you. Even without fault, the sponsor accepts responsibility for damage caused to the participant (or his/her dependants) and linked directly or indirectly to participation in this study. In this context, the sponsor has taken out an insurance contract (Amlin Europe NV, through mediation of Vanbreda Risks & Benefits NV, contract number 299.053.700, contact details: Vanbreda Risk & Benefits NV, Plantin en Moretuslei 297, 2140 Antwerp, tel +32 3 217 6767)[f].

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[c] For clinical studies, the law requires this link with your records to be retained for 20 years.

d The database containing the results of the study will therefore not contain any combination of elements such as your initials, your gender and your full date of birth (dd/mm/yyyy).

e The sponsor then undertakes to respect the constraints of the European Directive and the Belgian legislation on the protection of privacy.

[f] In accordance with Article 29 of the Belgian Law related to experiments on humans (7 May 2004)

1 ADAPTIVE SITUATION

In the sample size calculation, 2 scenarios are described: a scenario involving the recruitment of 300 physicians and a scenario with 220 physicians. In the protocol, all trial procedures are explained assuming 300 study physicians. In this appendix we describe an adaptive situation in case of a sample of 220 study physicians.

1.1 Sample size calculations

Sample size for comparison of 2 proportions (binary values): non-inferiority trial
Missed diagnoses: pA: 2.5%
Missed diagnoses: pA: 2.5%
Clinically significant change of 1%
$\alpha = 0.05$
$1-\beta = 0.80$
K = 1
Sample size: 6032
Sealed Envelope Ltd. 2012. Power calculator for binary outcome non-inferiority trial. [Online] Available from: https://www.sealedenvelope.com/power/binary-noninferior/ [Accessed Wed Jul 20 2016].
$DE = 1 + \rho(n-1)$
n = number individuals per cluster
ρ = intracluster correlation coefficient
We account only for the clustering on the level of the physician.
n = 42 for a trial lasting 3 months
n = 84 for a trial lasting 6 months
$\rho = 0.025$
for a trial lasting **3 months**: DE = 2.025 which implies **290 physicians (≈300 physicians)**
for a trial lasting **6 months**: DE = 3.075 which implies **220 physicians**

Figure 1: Sample size calculations for secondary outcomes missed or delayed diagnoses including inflation due to clustering

1.2 Trial design

In case of 220 included physicians: to recruit sufficient patients for our secondary outcome, an additional three months are required compared to the design including 300 physicians. During a period of nine months, intervention physicians will be exposed to our intervention and control physicians will not. After these twelve months, all physicians will be exposed to our intervention. These twelve months are sufficient to measure the effect of our intervention on a significant amount of patient contacts and laboratory test orders. Error! Reference source not found. illustrates the flow of the trial with 220 physicians included in the trial. We assume that recruiting 300 physicians is feasible and further references to trial design will refer to the first situation.

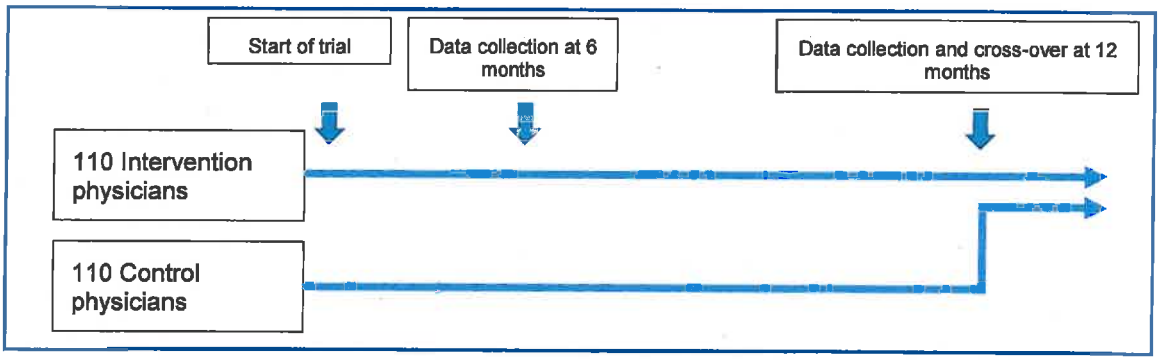

Figure 2: Flow of trial for appropriateness for sample of 220 physicians.

1.3 Trial procedures

Trial procedures in case of a sample of 220 physicians (110 physicians per arm)
Month 0-9 : participants involved designing and tailoring of the intervention, installing and configuring CPOE platforms, including usability testing, debugging and adjusting problems
Month 3-9 : physician recruitment
Month 8 : phase-in period of 1 month
Month 9: start study
Month 9-15 : intervention period in case of sample of 220 physicians
Month 15 : data collection for appropriateness in case of sample of 220 physicians
Month 12-18 : analysis data for appropriateness
Month 9-21 : follow-up of included patients in case of sample of 220 physicians
Month 9-21 : data collection through eCRF for possible diagnostic error (directly from study physicians)
Month 21-30 : chart reviews and patient interviews of participating patients for data collection for diagnostic error and downstream activities
Month 18-30 : mixed method process evaluation
Month 36-42 : drafting of reports on primary and secondary outcomes
Month 42-48 : drafting of economic evaluation (optional)

Figure 3: Trial procedures in case of a sample of 220 physicians.