

Change history

Version Nr	Version date	Modified without version change	Description, comments	Control
1.0	02.12.2021		Initial version	WH, TM
1.1	21.12.2021		Corrected few typos Change of monitoring institution Minor changes for clarification	WH, TM
1.2	25.01.2022		Changes as requested by Swissmedic and ethic committee based on submission v1.1	WH, TM
1.3	21.03.2022		Minor changes based on request of Swissmedic (Submission 2.0)	WH, TM
1.4	28.07.2022		<ul style="list-style-type: none"> - Specification of one inclusion criterion (7.1) - Extension of recruitment period and clarification when enrollment ends (7.2) - Adaption of monitoring plan (12.3) - Exchange of local PI at one site - Clarification of diagnostic discrepancy (9.2.1) - Clarification of protocol deviations within treatment intervention (9.3.2) - Clarification of patient follow-up and end of study (9.3.4) - Adjustment in PP-analysis 11.4.1 	WH, TM
1.5	10.10.2022		Undo adjustment in PP-analysis based on comment from Swissmedic Correction position of PI of Site Münsingen	WH, TM

Clinical Investigation Plan (CIP)

Study Title: Effects of digitalized differential diagnosis broadening using a computerized diagnostic decision support tool on diagnostic quality in emergency room patients - a multi-centre cluster randomized cross-over trial.

Short Title Digitalized differential diagnosis broadening in emergency rooms (DDX-BRO)

Type of investigation:	Clinical investigation concerning medical devices (MD).
Categorisation:	Risk category C2 according to Art 6 ClinO-MD
Registration:	Clinicaltrials.gov (anticipated registration in November 2021)
Identifier:	DDX-BRO
Sponsor-Investigator:	Prof. Dr. med Wolf Hautz Dept. of Emergency Medicine, Inselspital, University Hospital Bern Freiburgstrasse 16C, 3010 Bern, Switzerland wolf.hautz@insel.ch, +41 31 63 2 57 01
Sponsor representative (if the Sponsor is not located in Switzerland)	n.a
Medical Device:	<i>Isabel Pro- the DDx Generator</i> from Isabel Health Care
CIP Version and Date:	1.5, 10/10/2022

CONFIDENTIAL

The information contained in this document is confidential and the property of the Sponsor-Investigator. The information may not - in full or in part - be transmitted, reproduced, published, or disclosed to others than the applicable Competent Ethics Committee(s) and Regulatory Authority(ies) without prior written authorisation from the Sponsor except to the extent necessary to obtain informed consent from those who will participate in the investigation.

Signature Page(s)

ID number of the investigation: Clinicaltrials.gov NCT05346523

Title: Effects of digitalized differential diagnosis broadening using a computerized diagnostic decision support tool on diagnostic quality in emergency room patients - a multi-centre cluster randomized cross-over trial.

The Sponsor, the Principal Investigator and the Statistician have approved the CIP version 1.5, 10/10/2022 and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Sponsor-Investigator:

Place/Date

Signature

Principal Investigator at the local investigational site:

I have read and understood this CIP version 1.5, 10/10/2022, and agree to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Site: Dept. of internal and emergency medicine, Spital Münsingen

Principal investigator at the local investigational site: Dr. Med. Ines Griesshammer, Head Physician until 30.09.2022

Place/Date

Signature

Site: Dept. of internal and emergency medicine, Spital Münsingen

Principal investigator at the local investigational site: Dr. Med. Philipp Schönberg, Senior Physician from 01.10.2022 on

Place/Date

Signature

Principal Investigator at the local investigational site:

I have read and understood this CIP version 1.5, 10/10/2022, and agree to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Site: Dept. of Internal and Emergency Medicine, Buergerspital
Solothurn

Principal investigator at
the local investigational
site: Prof. Dr. med Gregor Lindner, Chief Physician

Place/Date

Signature

Principal Investigator at the local investigational site:

I have read and understood this CIP version 1.5, 10/10/2022, and agree to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Site: Dept. of Internal and Emergency Medicine, Spital Tiefenau

Principal investigator at the local investigational site: Dr. med Simon Johannes Bosbach, Head Physician

Place/Date

Signature

Table of Contents

SYNOPSIS	11
ABBREVIATIONS	15
SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS.....	17
INVESTIGATION SCHEDULE.....	17
1. INVESTIGATION ADMINISTRATIVE STRUCTURE	19
1.1 Sponsor, Sponsor-Investigator.....	19
1.2 Principal Investigator(s).....	19
1.2.1 Inselspital, University Hospital Bern.....	19
1.2.2 Spital Tiefenau Bern.....	19
1.2.3 Buergerspital Solothurn	19
1.2.4 Spital Münsingen.....	19
1.3 Statistician ("Biostatistician")	20
1.4 Qualitative Researcher	20
1.5 Laboratory	20
1.6 Monitoring institution	20
1.7 Data Safety Monitoring Committee	20
1.8 Any other relevant Committee, Person, Organisation, Institution	20
1.8.1 Steering Committee / Co-Investigators	20
1.8.2 Project management	20
1.8.3 CDDS implementation.....	21
1.8.4 Study nurse coordination	21
1.8.5 Mathematician.....	21
2. ETHICAL AND REGULATORY ASPECTS	21
2.1 Registration of the investigation	21
2.2 Categorisation of the investigation	21
2.3 Competent Ethics Committee (CEC)	21
2.3.1 Reporting duties to the Competent Ethics Committee.....	21
2.4 Art. 6 ClinO-MD (CA).....	21
2.4.1 Reporting duties to the competent authorities	22
2.5 Ethical Conduct of the Investigation	22
2.6 Declaration of interests.....	22
2.7 Patient Information and Informed Consent	22
2.8 Subject privacy and confidentiality	22
2.9 Early termination of the investigation	23
2.10 Clinical investigation plan amendments	23
2.11 Deviation from the Clinical Investigation Plan	23
3. BACKGROUND AND RATIONALE	24
3.1 Background and Rationale for the clinical investigation.....	24
3.2 Identification and description of the Investigational Medical Device	25
3.3 Preclinical Evidence	26
3.3.1 Accuracy	26
3.3.2 Potential impact on clinical decision making.....	26
3.4 Clinical Evidence to Date	27
3.5 Justification for the design of the clinical investigation.....	27

3.6	Explanation for choice of comparator.....	27
3.7	Risk evaluation (Risk-to-Benefits rationale)	28
3.8	Justification of the choice of the investigation population	28
4.	CLINICAL INVESTIGATION OBJECTIVES	29
4.1	Overall Objective	29
4.2	Primary Objective	29
4.3	Secondary Objectives	29
4.4	Safety Objectives	29
5.	CLINICAL INVESTIGATION OUTCOMES	30
5.1	Primary Outcome	30
5.2	Secondary Outcomes.....	30
5.3	Other Outcomes of Interest.....	30
5.4	Safety Outcomes.....	30
6.	CLINICAL INVESTIGATION DESIGN	31
6.1	General clinical investigation design and justification of design	31
6.2	Methods for minimising bias.....	32
6.2.1	Randomisation	32
6.2.2	Blinding procedures	32
6.2.3	Other methods for minimising bias	32
6.3	Unblinding Procedures (Code break).....	32
7.	CLINICAL INVESTIGATION POPULATION.....	33
7.1	Eligibility criteria.....	33
7.2	Recruitment and screening	33
7.3	Assignment to investigation groups	34
7.4	Criteria for withdrawal / discontinuation of subjects	35
8.	CLINICAL INVESTIGATION INTERVENTION	36
8.1	Identity of the medical device under investigation	36
8.1.1	Experimental Intervention (medical device)	36
8.1.2	Control Intervention (standard/routine/comparator)	37
8.1.3	Labelling and Supply (re-supply)	37
8.1.4	Storage Conditions.....	37
8.2	Discontinuation or modifications of the intervention.....	37
8.3	Compliance with clinical investigation intervention	37
8.4	Data Collection and Follow-up for withdrawn subjects	37
8.5	Clinical investigation specific preventive measures	37
8.6	Concomitant Interventions (treatments).....	38
8.7	Medical Device Accountability.....	38
8.8	Return, Analysis or Destruction of the Medical Device	38
9.	CLINICAL INVESTIGATION ASSESSMENTS	39
9.1	Clinical investigation flow chart(s) / table of clinical investigation procedures and assessments.....	39
9.2	Assessments of outcomes	40
9.2.1	Assessment of primary outcome.....	40
9.2.2	Assessment of secondary outcomes	41
9.2.3	Assessment of other outcomes of interest.....	41
9.2.4	Assessment of safety outcomes	41
9.2.5	Assessments in subjects who prematurely stop the clinical investigation	42

9.2.6	Follow-up of the subjects after the regular termination of the clinical investigation	42
9.3	Procedures at each visit	42
9.3.1	Screening	42
9.3.2	Consent (ICF).....	42
9.3.3	Treatment intervention period	43
9.3.4	Follow-up.....	43
10.	SAFETY	43
10.1	Definition and Assessment of (Serious) Adverse Events and other safety related events	43
10.2	Adverse events categorization	44
10.3	Documentation and reporting in Medical Device Category C clinical investigations	45
10.3.1	Foreseeable adverse events and anticipated adverse device effects	45
10.3.2	Reporting of (Serious) Adverse Events, device deficiencies, and other safety related events 46	
10.3.3	Follow-up of (Serious) Adverse Events.....	46
10.3.4	Reporting of Safety related events.....	Fehler! Textmarke nicht definiert.
10.4	Assessment, notification and reporting on the use of radiation sources.....	47
11.	STATISTICAL METHODS.....	48
11.1	Hypothesis.....	48
11.2	Determination of Sample Size.....	48
11.3	Statistical criteria of termination of the investigation	49
11.4	Planned Analyses.....	49
11.4.1	Datasets to be analysed, analysis populations.....	49
11.4.2	Primary Analysis	49
11.4.3	Secondary Analyses	50
11.4.4	Interim analyses	50
11.4.5	Deviation(s) from the original statistical plan	50
11.1	Handling of missing data and drop-outs.....	50
12.	QUALITY ASSURANCE AND CONTROL.....	50
12.1	Data handling and record keeping / archiving.....	50
12.1.1	Case Report Forms.....	50
12.1.2	Specification of source data and source documents	50
12.1.3	Archiving of essential clinical investigation documents	50
12.2	Data management.....	51
12.2.1	Data Management System	51
12.2.2	Data security, access and back-up	51
12.2.3	Analysis and archiving	51
12.2.4	Electronic and central data validation	51
12.3	Monitoring.....	51
12.4	Audits and Inspections	52
12.5	Confidentiality, Data Protection	52
12.6	Storage of biological material and related health data	52
13.	PUBLICATION AND DISSEMINATION POLICY.....	53
14.	FUNDING AND SUPPORT.....	54
14.1	Funding	54
14.2	Other Support.....	54

15. INSURANCE.....	54
16. REFERENCES.....	55
17. APPENDICES.....	59

SYNOPSIS

Sponsor / Sponsor-Investigator	Prof. Dr. med Wolf Hautz Dept. of Emergency Medicine, Inselspital, University Hospital Bern
Title:	Effects of digitalized differential diagnosis broadening using a computerized diagnostic decision support tool on diagnostic quality in emergency room patients - a multi-centre cluster randomized cross-over trial.
Short title / Investigation ID:	Digitalized differential diagnosis broadening in emergency rooms / DDX-BRO
Clinical Investigation Plan, version and date:	Version 1., 10/10/2022
Registration:	Clinicaltrials.gov NCT05346523
Category and its rationale:	Risk category C2 as the medical software under investigation does not carry a conformity mark according to Article 13 MedDO.
Name of the MD, Unique Device Identification (UDI), name of the manufacturer	<i>Isabel Pro- the DDx Generator</i> Isabel Healthcare Name of the manufacturer and the SRN number (Art. 31 MDR)
Stage of development:	Post market stage. The clinical investigation is not conducted for conformity assessment purpose.
Background and rationale:	Misdiagnosis occurs in about 5% of outpatients, and in 10% to 35% of emergency room (ER) patients, sometimes with devastating medical and economic consequences. Nowadays, there exists computerized diagnostic decision support programs (CDDS) which suggest differential diagnoses (DDx) to physicians and thus have potential to improve diagnosis and hence, outcomes of patient care. The effects of such CDDS in 'real-world' ER setting are unknown. Controlled clinical trials investigating their effectiveness and safety are absent. In addition, most available CDDS are overcautious and suggest a wide variety of diagnostic options, likely increasing diagnostic resource consumption.
Objective(s):	With this project, we aim to understand the intended and unintended consequences of CDDS use by physicians on diagnostic quality and workflow in emergency medicine on the micro-level , how CDDS affect diagnostic quality by physicians in individual emergency patients. on the meso-level , how CDDS affect the diagnostic workflow in emergency departments. on the macro-level , the economic and educational impact of CDDS utilization in ERs

Outcome(s):	<p>Primary (micro-level) outcome: A composite score indicating a diagnostic quality risk composed of death, unscheduled medical care, (both within 14 days), unexpected intensive medical care unit admission if hospitalized and diagnostic discrepancy between the ER discharge diagnosis and the current diagnosis after 14 days.</p> <p>Secondary outcomes will be all variables of the primary endpoint individually, unscheduled ER or general practitioner (GP) revisits after 72h and 7 days, length of ER and hospital stay, diagnostic tests, resource consumption in ER (costs), care consumption after ER discharge, discharge destination, patient reported outcomes, number and patterns of DDx provided by the physicians, number of cases where the generated DDx list entails the diagnoses after 14d, diagnostic error based on full chart review for a random subset, CDDS usage (timing and number of queries), physicians' confidence calibration, workflow indicators (such as contact time, throughput, advice seeking, and extent of collaboration)</p>
Design:	Single-blinded, cross sectional, multi-center, four-period cross-over controlled cluster-randomized trial
Inclusion / exclusion criteria:	<p>Key inclusion criteria will be presentation to the ER with fever, abdominal pain, syncope or a non-specific complaint as chief complaint.</p> <p>Key exclusion criteria will be triage assessment of "vitally threatened", trauma, pregnancy, worsening of a known pre-existing condition, admittance via police, psychiatric disease, and detainee status or unable to follow the informed consent or study procedure.</p>
Measurements and procedures:	<p>For the primary outcome, data will be extracted from the electronic health records (i.e. ER diagnosis, intensive medical care admission or diagnosis after 14d if patients were still hospitalized). Additionally, patients and their general practitioner will be contacted via telephone by the study nurses after 14d of study inclusion in order to prospectively collect information about patients' current diagnosis, re-visits or hospitalization related to the initial ER visit.</p> <p>Data for secondary endpoints will be retrieved from the routinely collected data in the electronic health record system (e.g mortality, time to ER diagnosis, resource consumption). Additionally, interviews and focus groups with physicians will be performed to investigate diagnostic workflow changes, physician confidence and other process outcomes.</p>

Intervention:	<p>Usual Care + CDDS.</p> <p>Patients presenting to the ER and included in the study during the ER's intervention period will be treated and diagnosed by the ER physicians as usual but with support of the CDDS. The treating resident physician will be asked to use the CDDS (Isabel Pro – the DDx generator) for each study participant included in the intervention period. After the first patient examination, the resident is asked to enter key symptoms into the CDDS, which will then return a list of 20 or more potential DDx matching the entered symptoms and patient characteristics. It is then free to the resident and attending physician to decide whether one or more of the suggested DDx should be considered for further diagnostic or treatment procedure based on clinical judgement.</p> <p><i>Isabel Pro – the DDx generator</i> from ISABEL healthcare ltd. is a web-based software that provides users with a list of potential DDx based on patient characteristics and key symptoms entered as free text. We will build our own web interface that is connected via application programming interface to ISABEL in order to achieve a smooth integration within the clinical workup of participating ERs and to track its usage.</p> <p>According to the manufacturer, Isabel Pro is considered as a generic search engine which matches symptoms to diseases and is not a probabilistic tool that attempts to come up with a diagnosis or list of diagnoses ranked by probability. The tool serves as reminder of possible DDx and aims to help clinicians with clinical reasoning in the same way as other websites like UpToDate, Dynamed, or Google. Therefore, the software has not been classified as medical device software by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) and thus, has no CE mark.</p>
Control intervention (if applicable):	Usual Care
Number of subjects with rationale:	74 patients per period and cluster and 1'184 patients in total are required to achieve sufficient power (see sample size calculation).
Duration of the investigation:	13 months
Investigation schedule:	<p>June 2022 – First-subject-In (planned)</p> <p>June 2023 - Last- subject-Out (planned)</p>

Investigator(s):	<p>Prof. Dr. med Wolf Hautz, Head of Research Dept. of Emergency Medicine, Inselspital, University Hospital Bern Freiburgstrasse 16C, 3010 Bern, Switzerland wolf.hautz@insel.ch, +41 31 63 2 57 01</p> <p>Dr. med Simon Johannes Bosbach, Head Physician Dept. of Internal and Emergency Medicine, Spital Tiefenau Tiefenaustrasse 112, 3004 Bern, Switzerland simonjohannes.bosbach@spitaltiefenau.ch, +41 31 308 86 48</p> <p>Prof. Dr. med Gregor Lindner, Chief Physician Dept. of Internal and Emergency Medicine, Buergerspital Solothurn Schöngrünstrasse 42, 4500 Solothurn, Switzerland notfallsekretariat.bss@spital.so.ch, +41 32 627 43 28</p> <p>Dr. med. Ines Griesshammer, Head Physician, until 30.09.2022 Dept. of internal and emergency medicine, Spital Münsingen Krankenhausweg 18/20, Postfach 2003, 3110 Münsingen, Switzerland ines.griesshammer@spitalmuensingen.ch, +41 31 682 82 93</p> <p>Dr. med. Philipp Schönberg, Senior Physician, from 01.10.2022 on Dept. of internal and emergency medicine, Spital Münsingen Krankenhausweg 18/20, Postfach 2003, 3110 Münsingen, Switzerland Philipp.schoenberg@spitalmuensingen.ch, +41 31 682 82 93</p>
Investigational Site(s):	<p>Multicentric investigation:</p> <ul style="list-style-type: none"> - Emergency Department, University hospital of Bern, Inselspital Bern - Dept. of Internal and Emergency Medicine, Spital Tiefenau - Dept. of internal and emergency medicine, Spital Münsigen - Dept. of Internal and Emergency Medicine, Buergerspital Solothurn
Statistical considerations:	<p>Statistical analysis will be based on multi-level general linear mixed modelling (GLMM) methods using appropriate post hoc techniques (e.g for subgroup analyses).</p> <p>For the primary outcome (presence or no presence of a positive diagnostic quality risk score), a generalized linear mixed model (GLMM) with a binomial distribution family and exchangeable correlation structure will be performed. The GLMM takes into account a random effect for each site, resident and attending physician. Diagnosing resident and attending physicians are nested within sites. The condition (intervention and control) and the period (period 1 to 4) will be included as fixed factors under the assumption of equality of carry-over effects. Additionally, presenting chief complaint, patient's age, sex and comorbidity index will be added as covariates.</p> <p>For all secondary endpoints, summary statistics appropriate to the distribution will be tabulated by treatment group. Analysis of secondary endpoints will parallel the primary analysis.</p>
Compliance statement:	<p>This investigation will be conducted in compliance with the CIP, the current version of the Declaration of Helsinki, ISO14155, ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements.</p>

ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
ASR	Annual Safety Report
CA	Competent Authority (e.g. Swissmedic)
CDS	Clinical decision support systems
CDDS	Computerized diagnostic decision support program
CEC	Competent Ethics Committee
CIP	Clinical investigation plan
ClinO	Ordinance on Clinical Trials in Human Research (<i>in German KlinV, in French Oclin, in Italian OSRUm</i>)
ClinO-MD	Ordinance on Clinical Trials with Medical Devices (<i>in German: KlinV-Mep, in French: Oclin-Dim, in Italian: OSRUm-Dmed</i>)
CR	clinical routine
CRF	Case Report Form (pCRF paper CRF; eCRF electronic CRF)
DD	Device Deficiency
DDx	Differential diagnoses
DMC / DSMC	Data Monitoring Committee, Data Safety Monitoring Committee
EDC	Electronic data capturing
EHR	Electronic health record
ER	Emergency Room
GLMM	Generalized linear mixed model
GP	General practitioner
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings (<i>in German: HFG, in French: LRH, in Italian: LRUM</i>)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation – guidelines of Good Clinical Practice
ICU	Intensive care unit
IFU	Instruction For Use
ISF	Investigator Site File
ISO	International Organisation for Standardisation
ITT	Intention to treat
LOS	Length of stay
MHRA	Medicines and Healthcare products Regulatory Agency
MedDO	Medical Devices Ordinance (<i>in German: MepV, in French: Odim, in Italian: Odmed</i>)

MD	Medical Device
MDR	Medical Device Regulation (EU) 2017/745 of 5 April 2017
NSC	Non-specific complaint
PI	Principal Investigator
PP	Per protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SNCTP	Swiss National Clinical Trials Portal
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr, Version Date	Chapter	Description of change	Reason for the change

INVESTIGATION SCHEDULE

Investigation Periods	Screening	Consent (ICF)	Treatment, Intervention Period		Follow-up
Emergency Care in the emergency room	Admittance and Triage	Waiting Time	Medical examination and treatment		discharged or hospitalized
Time	-1 to -5h	-1 to -5h	0 to 1h	1h + LOS	14d±4d
A) Enrolment					
In- /Exclusion Criteria	x				
Patient information		x			
Patient consent (ICF)		x			
B) Intervention					
CDDS application during intervention period			x	(x)	
CDDS usage monitoring by study nurses			x		
C) Assessments (CR: performed within clinical routine as appropriate)					
Demographics	x				
Chief complaint	CR				
Triage assessment	CR				
Medical history			CR		
Physical examination			CR	CR	
Vital signs			CR	CR	
Laboratory tests			CR	CR	
Other diagnostic tests			CR	CR	
CDDS input / output data collection			x	(x)	
Physician questionnaire			x	(x)	
Patient telephone interviews					x
Medical record review from ER, hospital and/or GP			x	x	x
Serious Adverse Events, Adverse device effects			x	x	x
Device Deficiencies			x	x	
D) Primary Outcome Score					
All-cause mortality					x

Unscheduled medical care if discharged (GP, ER revisit, hospitalization)					x
Unexpected ICU admission within 24h if hospitalized					x
Current diagnosis for presenting complaint				x	x
E) Secondary Outcomes					
Number and cost of ER diagnostic tests				x	x
Time to ER diagnosis				x	
ER differential diagnoses				x	
Physician confidence in ER diagnosis				x	
Discharge destination				CR	
ER LOS				CR	
Hospital LOS if hospitalized					CR
CDDS usage (number of queries)			x	(x)	
Patient reported outcomes					x
ER, Emergency room; ICU, intensive care unit; CDDS, computerized diagnostic decision support system; GP, general practitioner; LOS, length of stay; CR, clinical routine					

1. INVESTIGATION ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

Prof. Dr. med Wolf Hautz, Head of Research

Dept. of Emergency Medicine, Inselspital, University Hospital Bern

Freiburgstrasse 16C, 3010 Bern, Switzerland

wolf.hautz@insel.ch, +41 31 63 2 57 01

Sponsor-investigator and PI, main responsible person of the investigation design, study management and data analysis and interpretation, overseeing the trial at University Hospital of Bern and Coordinator of other centers

1.2 Principal Investigator(s)

1.2.1 Inselspital, University Hospital Bern

Prof. Dr. med Wolf Hautz, Head of Research

Dept. of Emergency Medicine, Inselspital, University Hospital Bern

Freiburgstrasse 16C, 3010 Bern, Switzerland

wolf.hautz@insel.ch, +41 31 63 2 57 01

Sponsor-investigator and PI, main responsible person of the investigation design, study management and data analysis and interpretation, overseeing the trial at University Hospital of Bern and Coordinator of other centers

1.2.2 Spital Tiefenau Bern

Dr. med Simon Johannes Bosbach, Head Physician

Dept. of Internal and Emergency Medicine, Spital Tiefenau

Tiefenaustrasse 112, 3004 Solothurn, Switzerland

simonjohannes.bosbach@spitaltiefenau.ch, +41 31 308 86 48

PI, main responsible person overseeing trial at Spital Tiefenau

1.2.3 Buergerspital Solothurn

Prof. Dr. med Gregor Lindner, Chief Physician

Dept. of Internal and Emergency Medicine, Buergerspital Solothurn

Schöngrünstrasse 42, 4500 Solothurn, Switzerland

notfallsekretariat.bss@spital.so.ch, +41 32 627 43 28

PI, main responsible person overseeing trial at Buergerspital Solothurn

1.2.4 Spital Münsingen

Dr. Med. Ines Griesshammer, Head Physician, until 30.09.2022

Dr. med. Philipp Schönberg, Senior Physician, from 01.10.2022 on

Dept. of internal and emergency medicine, Spital Münsingen

Krankenhausweg 18/20, Postfach 2003, 3110 Münsingen, Switzerland

ines.griesshammer@spitalmuensingen.ch, +41 31 682 82 93

Philipp.schoenberg@spitalmuensingen.ch, +41 31 682 82 93

PI, main responsible person overseeing trial at Spital Münsingen

1.3 Statistician ("Biostatistician")

Prof. Dr. Stefan Schaubert,
Centre for Health Sciences Education, Faculty of Medicine, University of Oslo
Gaustadalléen 30D, Postboks 1078, 0316 Oslo, Norway
stefan.schauber@medisin.uio.no, +47 22850225

Dr. Thimo Marcin
Dept. of Emergency Medicine, Inselspital, University Hospital Bern
Freiburgstrasse 16C, 3010 Bern, Switzerland
thimo.marcin@extern.insel.ch, +41 31 664 11 80

Statistical counselling will be requested from the Clinical Trial Unit Bern, Switzerland

1.4 Qualitative Researcher

Dr. rer. Medic Stefanie Hautz, MME
Dept. of Emergency Medicine, Inselspital, University Hospital Bern
Freiburgstrasse 16C, 3010 Bern, Switzerland
stefanie.hautz@extern.insel.ch, +41 31 664 11 80

1.5 Laboratory

Laboratory institutes of the local ER hospital.

1.6 Monitoring institution

Department of Neurosurgery, Inselspital, Bern University Hospital, University of Bern

1.7 Data Safety Monitoring Committee

No Data Safety Monitoring Committee is intended for this study as there is no harm expected that is directly caused by the medical device software under investigation and because the investigation of indirect harm caused by applying the medical device software in clinical routine is the primary objective of this study.

1.8 Any other relevant Committee, Person, Organisation, Institution

1.8.1 Steering Committee / Co-Investigators

Prof. Wolf Hautz, Sponsor-Investigator
Prof. Aristomenis Exadaktylos, President, Swiss Society of Emergency Medicine
Prof. David Schwappach, Director, Patient Safety Switzerland. Professor of Patient Safety at Institute for Social and Preventive Medicine, University of Bern
Prof. Hardeep Singh, Director: Diagnosis Improvement Safety Center (DISCOVERY), Houston, Tx
Prof. Laura Zwaan, Assistant Professor, Institute of Medical Education, ErasmusMC Rotterdam
Prof. Sissel Guttormsen, Director, Institute for Medical Education, University of Bern
Prof. Mathieu Nendaz, Director of the Unit of Development and Research in Medical Education and Department of Medicine, Faculty of Medicine, Geneva
Prof. Thomas Sauter, Assistant Professor of Teleemergency Medicine, Inselspital University Hospital Bern

1.8.2 Project management

Dr. Stefanie Hautz, Co-lead, Diagnostic Decision Support, Dept. of Emergency Medicine, Inselspital University Hospital

Dr. Thimo Marcin, Co-lead, Diagnostic Decision Support, Dept. of Emergency Medicine, Inselspital University Hospital

1.8.3 CDDS implementation

Dr. Gert Krummery, attending physician and medical informatics specialist

1.8.4 Study nurse coordination

Cornelia Lambrigger, Head study nurse, Dept. of Emergency Medicine, Inselspital University Hospital

1.8.5 Mathematician

PD Dr. med. Dipl. Math. Martin Müller, PhD, MSc, Dept. of Emergency Medicine, Inselspital University Hospital

2. ETHICAL AND REGULATORY ASPECTS

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the European Regulation on medical devices 2017/745 and the ISO Norm 14155 and ISO 14971 and the Swiss Law and Swiss regulatory authority's requirements.

The Sponsor-Investigator declares no conflicts of interests.

The final positive decision of the CEC and of the CA on the conduct of the investigation will be made and given in writing to the Sponsor before the investigation can start. In Switzerland the national approval for the present category C study is issued by Swissmedic and includes the approval of the CEC.

2.1 Registration of the investigation

The study will be registered in the Clinical Trials Registry Platform of the National Institute of Health (NIH) – ClinicalTrials.gov (anticipated in February 2022)). In addition, the trial will be registered in the Swiss National Clinical Trials Portal (SNCTP).

2.2 Categorisation of the investigation

Risk category C2.

The medical software under investigation does not carry a conformity mark according to ClinO-MD, Art.6, Abs 3b

2.3 Competent Ethics Committee (CEC)

The Sponsor-Investigator will submit the investigation to the CEC and obtain ethical committee approval before the start of the investigation. Each PI at each participating investigational site ensures that approval from the CEC is obtained and filed in the Investigator site file before the investigation starts.

2.3.1 Reporting duties to the Competent Ethics Committee

Amendments are reported according to Art. 15 ClinO-MD (see also 2.10).

The regular or premature end of the investigation as well as the interruption of the investigation is reported to the CEC within 15 days (within 24 hours if it is due to security reasons) (Art. 36 ClinO-MD). The reasons for a premature end or an interruption have to be explained.

A final report shall be submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation (Art. 37 ClinO-MD).

No changes are made to the CIP without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to subjects according to chapter 10 for safety reporting.

2.4 Art. 6 ClinO-MD (CA)

The Sponsor-Investigator will submit the investigation to the CA and obtain regulatory approval before the start of the investigation. Each PI at each participating investigational site ensures that approval from the CA is obtained and filed in the Investigator site file before the investigation starts.

2.4.1 Reporting duties to the competent authorities

Amendments are reported according to Art. 20 ClinO-MD.

The regular or premature end of the investigation as well as the interruption of the investigation is reported to the CA within 15 days (within 24 hours if it is due to security reasons) (Art. 36 ClinO-MD). The reasons for a premature end or an interruption have to be explained.

A final report shall be submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation (Art. 37 ClinO-MD).

No changes are made to the CIP without prior Sponsor and CA approval, except where necessary to eliminate apparent immediate hazards to subjects according to chapter 10 for safety reporting.

2.5 Ethical Conduct of the Investigation

The investigation will be carried out according to the CIP and with principles enunciated in the current version of the Declaration of Helsinki, the European Regulation on medical devices 2017/745 (MDR), the Norms ISO14155 and ISO14971, the ICH-guidelines of Good Clinical Practice (GCP) as applicable, the Swiss Human Research Act (HRA) and its Ordinances and Swiss regulatory authority's requirements. The CEC and the CA will receive the Annual Safety Report (ASR) and interim reports and be notified about investigation stop/end in agreement with local requirements.

2.6 Declaration of interests

The Sponsor-Investigator declares no conflict of interest with the conduct of this trial.

2.7 Patient Information and Informed Consent

A designated study nurse explains to each subject the nature of the investigation, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject is informed that the participation in the investigation is voluntary and that he/she may withdraw from the investigation at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The subjects are informed that he/she can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their participation in the investigation. The study takes place in an emergency setting, however, only patient triaged as "non-vitally threatened" are eligible. The waiting time from admittance to first examination by a physician in non-vitally threatened patients takes usually >1 hour, depending on the ER crowding. The informed consent procedure takes place within this timeframe providing enough time to elucidate the will of the subject without leading to a delay in patient care. If necessary, time for inclusion can be prolonged up to 1 hour after first patient examination and before the intervention (i.e CDDS query) should be performed (see chapter 8.1.1)

The subjects are informed that authorised individuals other than their treating physician may examine his/her medical records.

All subjects are given a subject information sheet and a consent form describing the investigation and providing sufficient information for the subjects to make an informed decision about their participation in the investigation.

The formal consent of a subject, using the approved consent form, is obtained before the subject is submitted to any investigation procedure.

The subject should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the subject and the PI (or her/his designee). The signed consent form is retained as part of the investigation records.

2.8 Subject privacy and confidentiality

The Sponsor and the PI affirm and uphold the principle of the subjects' right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the subjects shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this investigation is considered confidential and disclosure to third parties is prohibited.

The assignment of a unique subject identification number to each subject ensures subject confidentiality.

The study number will consist of a four-digit number of the site and an ascending number of the included

patient for the respective site (e.g. 2899-1, 2899-2, 2899-3 ...) created upon registration of the consecutively recruited study participant (see section 12.5 Confidentiality, Data Protection).

For data verification purposes, authorised representatives of the Sponsor, the CA or a CEC may require direct access to parts of the medical records relevant to the investigation, including subjects' medical history. The PIs will permit investigation-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) and grant direct access to source data and documents on such occasions.

2.9 Early termination of the investigation

The Sponsor-Investigator may terminate the investigation prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient subject recruitment,
- when the safety of the subjects is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of the investigation unwise,
- early evidence of benefit or harm of the experimental intervention.

2.10 Clinical investigation plan amendments

Any amendments made to the CIP must be approved by the Sponsor-Investigator. Responsible investigators of other trial sites as well as members of the steering committee may provide suggestions for a protocol amendment. All site PIs and members of the steering committee will be informed about amendments and changes in the CIP.

Substantial amendments are only implemented after approval by the CEC (Art. 15 ClinO-MD) and, for category C investigations, after approval by the CA also (Art. 20 ClinO-MD). The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of the subjects may proceed without prior approval by the Sponsor and the CEC (and for category C investigations without prior approval by the CA). Such deviations shall be documented and reported to the Sponsor and the CEC (and to the CA for category C investigations) within 2 days (Art. 34 ClinO-MD).

All non-substantial amendments are communicated to the CEC together with the Annual Safety Report (ASR) (Art. 15 ClinO-MD), and for category C clinical investigations to the CA as soon as possible (Art. 20 ClinO-MD). The ASR shall include any deviations from the CIP that may have affected the rights, safety or well-being of the subject or the scientific integrity of the investigation (ISO14155).

2.11 Deviation from the Clinical Investigation Plan

The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Working instructions will be provided to involved study personal to prevent CIP deviations. Designated local study nurses will be responsible to support diagnosing physicians in CDDS usage and to assure that they follow the CIP procedures. CIP deviations will be documented in the eCRF by the study nurse. CIP deviations will be analysed and reported in the final report.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale for the clinical investigation

Diagnostic error in emergency medicine

Getting the right diagnosis is a key aspect of health care - it provides an explanation of a patient's health problem and informs subsequent health care and treatment. Misdiagnosis occurs in about 5% of outpatients, and in 10% to 35% of emergency room (ER) patients, sometimes with devastating medical and economic consequences.(1–9) The causes for diagnostic error can be diverse, but one major cause is human error. This includes the consideration of incomplete histories, failure to consider alternatives, lack of knowledge and lack of recognition of clinical findings by physicians.(5,10–13) An accurate diagnosis is the basis for all treatment and care and hence, improving the diagnostic process and accuracy key to improve patient safety and outcome.

Clinical decision support systems

Within the last decades, digitalization in health care has led to a rapid evolution of various clinical decision support systems (CDS) supposed to augment clinicians in their complex decision-making processes.(14) A recent systematic literature review on electronic health record (EHR) integrated CDS in the ER found positive effects on various outcomes in 83% of the included articles.(15) However, the included CDS types, targets and measured outcomes were heterogeneous and the included studies of mixed quality. CDS that were built to support clinicians specifically in the process of diagnosis (computerized diagnostic decision support system; CDDS) have not shown such promising results as other types of CDS so far, mostly due to negative physician perception and biases, poor accuracy or poor system integration.(14)

Differential diagnosis

A key role in the diagnostic process has been attributed to differential diagnoses (DDx) as they guide physicians in considering or excluding possible diagnoses in the ongoing diagnostic process.(16) Research in primary care found that in absence of a correct diagnostic hypothesis, physicians tried to explain evidence away that did not fit their diagnosis and that misdiagnosis occurred most when the correct diagnosis was not even considered.(17,18) Broadening the differentials has been consistently recognized as important measure to avoid diagnostic errors in primary care.(19,20) However, diagnostic hypothesis generation in the ER is often based on physician intuition and linked to past experience.(21) Given the vast amount of diseases and clinical manifestations that ER physicians are confronted with, they cannot be expected to think of all possible DDx. It is likely that they either do not recall or know all of the potential DDx fitting the clinical presentation and symptoms.

DDx Generators

Reminding physicians of potential DDx is the aim of DDx generators. This form of CDDS were firstly developed in the 1970s.(22) DDx generators are built to provide physicians with a list of DDx based on clinical data input such as patient characteristics, symptoms, findings and other factors.

DDx generators have continued to evolve in the last decades as computational methods have advanced. Nowadays, DDx generators are capable of matching input data to large electronic databases of diagnoses using varying computational methods such as Bayesian probabilities or text mining techniques(23) to subsequently retrieve the correct diagnosis with a considerably high accuracy. Likewise, integration in EHR systems has improved continuously and thus, enhancing usability in clinical practice.(14)

Accuracy of DDx generators

A systematic review and meta-analysis from 2016 investigating the efficacy and utility of DDx generators found a high accuracy in diagnosis retrieval with a pooled rate of 0.7, meaning that the correct diagnosis was in 70% of the cases among the provided DDx. However, usage of DDx generators did not demonstrate improved diagnostic retrieval and only small improvements were seen in the before and after studies where clinicians had the opportunity to revisit their diagnoses following a DDx generator consultation.(23) However, most of the included studies were considered to be at high risk for selection, funding and publication bias and the findings of some older included studies may not be applicable to the DDx generators nowadays given their improved accuracy and usability. Most importantly, DDx

generators were applied retrospectively across the majority of the studies, reducing the external validity of the results.

Effectiveness of DDx generators and knowledge gaps

To the best of our knowledge, studies investigating the effectiveness and safety of DDx generators in 'real world' setting are absent. Therefore, it is unknown to what extent the use of these CDDS actually improve the quality of medical diagnoses and consecutive health outcomes of the individual patient (micro-level effects). In addition, research indicates that collaboration in health care is frequent and substantially improves diagnostic accuracy.(4,24,25) CDDS may lower ER physician's perception whether they need advice and thus reduce the likelihood of collaboration. The effect of a DDx generator on physicians' diagnostic workup of and ER collaboration in general are widely unclear (meso-level effects). Furthermore, previous research has indicated that CDDS usage results in increased diagnostic investigations and higher costs.(26–28)

Considering rare differential diagnoses suggested by CDDS for patients presenting with common symptoms may trigger extensive (and expensive) additional testing that would not be conducted otherwise. Whether changes on the micro- or meso-level justifies the potentially increasing costs in our health care system (macro-level effects) remains to be decided upon by society. Currently, we lack evidence to inform such a debate.

Aims

Therefore, we aim 1) to assess the effect of the DDx generator usage on diagnostic quality in patients admitted to ER, 2) to understand the influence that DDx generators have on the physicians' diagnostic workflow and the workup in the emergency departments in general and 3) to investigate the effect of the DDx generator on resource utilization and costs.

3.2 Identification and description of the Investigational Medical Device

The software under investigation is "Isabel Pro - the DDx Generator" from ISABEL Healthcare Ltd. The German version will be used in the present study. Isabel Pro is developed for health professionals, i.e. the software is intended to support clinicians in broadening their differential diagnoses in the diagnostic workup.

The web-based software provides users with a list of potential DDx based on patient characteristics and key symptoms entered as free text. Isabel includes a thesaurus with predictive terms that facilitates the text entry via an autocomplete function. Isabel Pro uses then statistical natural language processing to match the entered clinical data onto a database of more than 10'000 diagnoses (i.e. more than 6'000 diseases and 4'000 drugs) to identify those diagnoses that are possibly relevant to the entered data. The database is manually built over the last decades by using various sources and is now updated every 2 to 4 weeks. Additionally, robust algorithms are in place to improve the queries (e.g. synonyms of the entered clinical data are searched in an extensive synonym file) or to filter the output so that results are relevant for patients' age, sex and region. Within the German version of Isabel Pro, additional algorithms are in place to translate the entered data from German into English and subsequently search the English database in case of clinical terms are not found in the German database in first place. More details on the software are provided in the Investigator Brochure (IB).

According to the manufacturer, Isabel Pro is considered a generic search engine simply matching symptoms to diseases and not a probabilistic tool that attempts to come up with a diagnosis or list of diagnoses ranked by probability. Therefore, the intended purpose of the tool is to serve as reminder of potential DDx and subsequently help clinicians with clinical reasoning in the same way as other websites such as UpToDate, Dynamed, or Google do. Accordingly, the software has not been classified as medical device software by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) and hence, has no CE mark.

Isabel Pro can be used as stand-alone web-tool or be integrated in nearly every EHR system or workflow management system. We will build our own web interface which will query Isabel Pro via application programming interface (API). This will allow us to achieve a smooth as possible integration within the clinical workup of the participating ERs and to have full control of usage and data entry. This interface follows the recommendation of the manufacturer and is described in detail in chapter 8.1

Recommendations for usage is provided in the IB. Isabel healthcare provides training video of 3-5 minutes length and 2-3 slides with tips for usage. We will additionally provide a short instruction for use regarding our interface. All residents will additionally be briefed by a designated study nurse before first

usage and the local study nurse will accompany the resident physician during the first query and remains contact persons for upcoming usability questions of the physicians. The designated local study nurses will be trained prior to the start of the intervention by the project leaders and training will be documented in the trial master file.

3.3 Preclinical Evidence

Isabel has undergone a continual robust and peer-reviewed validation process over the last 20 years with published peer-reviewed articles to demonstrate Isabel Pro's accuracy and impact on clinical decision-making, mostly on simulated or retrospective cases outside of the clinical routine.

3.3.1 Accuracy

One of the first studies on diagnostic accuracy retrieval was performed in 2003 on 99 hypothetical paediatric cases provided by clinicians and 100 documented cases of children admitted to acute paediatric. Isabel displayed the correct diagnosis in 91% and 95% of the hypothetical and real cases respectively.(29) In a comparable study, key clinical and laboratory findings from the admission notes and data obtained within first 30min investigation after patients' admission to the pediatric intensive care unit were entered into Isabel. The tool provided the final diagnosis for 80.5% of the 200 patients.(30)

A multi-center study investigated Isabel's diagnostic accuracy retrieval on 594 patients presenting to emergency departments with acute medical problems and hospitalized thereafter. Clinical data was extracted from patient notes available of the first examining clinician and entered into the software. Isabel displayed the final hospital discharge diagnosis in 95% of the cases. (31)

In another validation study, Isabel was tested on 50 internal medicine case records published in the New England Journal of Medicine. Isabel provided the correct diagnosis in 96% of the cases when only key findings were entered and in 74% of the cases when the entire case history was pasted into the system.(32)

Bond et al (2012) evaluated 23 different computer programs that generate DDx based on clinical data using 20 test cases (derived from the case records of the New England Journal of Medicine and from the Medical Knowledge Self-Assessment Program) on each of the programs. The investigator evaluated the performance with a scoring system ranging from 0 to 5, with 0 indicating that none of the suggestions was close to the correct diagnosis and 5 indicating the presence of the exact diagnosis. Isabel has shown the best performance among the investigated programmes with a mean score of 3.45.(33)

Finally, a recent systematic review and meta-analysis found that Isabel showed the highest pooled accurate diagnosis retrieval rates among all the reviewed DDx generating computer programmes with a pooled diagnostic accuracy rate of 89% (95% CI 0.83 to 0.94).(34)

The German version that will be used in the clinical investigation was developed in 2021 and has now been validated against 50 vignettes derived from a German text book on emergency room cases and on 50 emergency room patient records derived from the electronic health record system of a German speaking university hospital in Switzerland. Overall, the correct diagnosis was provided in 82% of the cases, indicating a comparable diagnostic accuracy retrieval rate as shown by the studies on the English version. [unpublished – in preparation]

3.3.2 Potential impact on clinical decision making

A systematic review from 2016 summarized studies on the impact of different DDx generating software tools on users' diagnostic lists and reported 6 studies showing an increase in the length of the diagnostic list, one study indicating a decline in the quality of diagnostic lists after consultation of the software and one study showing no impact. (34) Following studies were performed using the system from Isabel Healthcare.

Ramnarayan et al. (2006) found a reduction of diagnostic errors (i.e failure of considering all clinically important diagnoses) in a quasi-experimental study, where 76 clinicians of various grades made a clinical decision regarding differential diagnoses, test-ordering and treatment for 24 simulated cases before and after Isabel consultation. (35)

Further studies looking into the impact on diagnosis decision making before and after use of Isabel have been carried out independently of Isabel developers. Medical students who self-reported the use of Isabel showed greater success in finding the correct diagnosis for simulated patient cases (36). Likewise, diagnostic reasoning of medical students improved from before to after Isabel consultation during simulated encounters.(37)

A more comprehensive study investigated the value of Isabel on 161 patients admitted to paediatric

Intensive Care Units without an established diagnosis. Independent paediatric intensivists consulted Isabel by entering clinical data available at time of admission in order to expand the initial DDx list of the admitting team with possible clinical relevant diagnoses selected from Isabel's DDx list. The admitting team's differential list contained the final discharge diagnosis in 89.4% of the cases. The DDx from the attending intensivist combined with the DDx from the admitting trainee team provided the diagnosis in 92% of the cases before consulting Isabel and in 95% after consulting Isabel. The attending intensivist was able to identify the relevant DDx provided by Isabel in 2 of 5 cases where the admitting Team initially failed to provide the correct diagnosis.(38)

A very recent study investigated the impact of early and late Isabel usage within the diagnostic process on number of DDx and diagnostic accuracy. Sixty-seven medical students, 62 residents and 61 practicing physicians in internal or emergency medicine were randomized to use Isabel on sixteen written cases based on actual cases either after receiving only chief complaint and demographic information or after all case information were provided. Early use of Isabel resulted in a greater number of differential diagnoses compared to late use (2.32 vs 0.89). In contrast, the correct diagnosis was more likely to be present in the list of differential diagnoses when Isabel was consulted late in the diagnostic process. Nevertheless, improved diagnostic accuracy after Isabel consultation was observed in both groups (7% for early usage and 8% for late usage).(39)

3.4 Clinical Evidence to Date

While Isabel's performance and potential impact on diagnostic quality has extensively been investigated on simulated or retrospective patient cases, few studies evaluated Isabel in a clinical routine setting.

Ramnarayan et al. (2006) provided the tool to junior doctors of paediatric ambulatory units and observed usage and clinical decisions regarding differential diagnosis, test ordering and treatment before and after the consultation of Isabel. An expert panel of independent paediatric consultants reviewed the cases and found a reduction in diagnostic workups construed as unsafe from before (45.2%) to after (32.7%) Isabel consultation. In 9.3% of the cases, at least one significant investigation was added to the management plan after Isabel consultation. Overall, clinicians attempted to use Isabel in 8.6% of all medical assessments, however, because of numerous technical barriers, diagnostic advice was examined for only 30% of these cases. Also, no adverse effects on patient management following Isabel consultation were observed. The number of differential diagnoses and ordered tests increased somewhat after Isabel usage, however, no deleterious tests nor treatments were added after Isabel advice. In addition, no clinically significant differential diagnoses were deleted from the diagnostic workup after Isabel consultation. (8)

In addition, no reports of an increase in diagnostic test ordering were reported since Isabel's launch in 2001 according to the manufacturer,

To the best of our knowledge, there is no randomized clinical controlled trial so far that investigated the effect of a DDx generator on diagnostic safety in a real-world clinical setting.

3.5 Justification for the design of the clinical investigation

Choice of Isabel Pro as DDx-Generator

Diagnoses are most likely not improved by CDDS if generated DDx list do not entail the correct diagnosis.(40) Therefore, a high accuracy in diagnosis retrieval is key for a DDx generating CDDS. A systematic review and meta-analysis found that Isabel Pro was associated with the highest rates of accurate diagnosis retrieval among the investigated CDDS (pooled rate = 0.89, 95% CI = 0.83 to 0.94; I² = 82%, p<0.001).

To be used in clinical routine, a CDDS should be of easy and fast to use, especially in emergency medicine where time is scarce. Isabel Pro is simple to use and time to enter data and obtain diagnostic suggestion takes less than a minute.(32) Additional factors supporting the choice of Isabel Pro as DDx Generator for our study is the facilitated integration in the workflow management software and the available German interface.

The general design of the study and its justification is described in detail in chapter 6.

3.6 Explanation for choice of comparator

Study patients presenting to an ER while this ER is in the control period will be diagnosed without CDDS support according to established local practice. The CDDS will only be available during intervention

periods.

Using another DDx generator as comparator would prevent conclusion on changes in the diagnostic process (see section 4.3 Secondary Objectives). Applying a sham MD (e.g. a DDx generator suggesting only wrong DDx) is considered unethical by misleading clinicians and subsequently putting patients at risk for misdiagnosis and unnecessary diagnostics.

3.7 Risk evaluation (Risk-to-Benefits rationale)

There is no harm expected that can directly be caused by the use of the DDx generator. However, the consideration of differential diagnoses suggested by CDDS for patients presenting with common symptoms may trigger additional testing that would not be conducted otherwise, hence, posing patients at risk for over-diagnosing. Some of the diagnostic tests may even be potentially harmful for patients (e.g. CT scans). Furthermore, the provided DDx may mislead physicians in the diagnosis finding, especially if the correct diagnosis is not included in the generated DDx list. Therefore, the CDDS query may lead to a prolongation in the diagnostic workup in some of the patients.

However, whether DDx provided by the CDDS should be considered for further testing (and treatment) is solely decided by the treating physicians based on clinical judgement. Examination of expensive or potentially harmful testing is always in the responsibility of the experienced attending physician who will ensure that only clinically relevant diagnostic tests are performed during ER stay.

Vice versa, DDx generators may potentially alert physicians to the correct diagnosis they would not think of in first place and therefore, reducing misdiagnosis, unnecessary and even potentially harmful testing or specialist consultation. This would directly benefit the patient, both in less harmful testing and in treatment. This would have an immediate benefit for the patient undergoing treatment.

We believe that the potential benefit exceeds the potential risk for the individual participating patient. Moreover, the present study provides data for the first time to inform this very debate of risk-benefit assessment regarding use of CDDS in a real world ER setting.

3.8 Justification of the choice of the investigation population

Misdiagnosis occurs in about 5% of outpatients, and in 10% to 35% of ER patients.(1–9) Prevalence of diagnostic errors may be especially high in health care setting where physicians have the challenging task to identify patients with a serious disease from a large sample of patients who present with common symptoms and often benign diseases.(41) The spectrum of diseases that physicians are confronted with in ERs is broad. Together with the time pressure that often prevails and may prevent physicians from broadening differential, ERs are particularly suitable as setting for the intended intervention. Moreover, there is a substantial amount of ER patients presenting with non-specific complaints which are associated with increased ER and hospital length of stay, mortality as well as time and resource consumption.(42) Therefore, the present study includes patients presenting to the ER with fever, abdominal pain and syncope as chief complaint, because all these complaints occur frequently, can result from a large number of underlying diseases and thus provide room for error. Additionally, patients with non-specific complaints will be included as they receive more often unspecific diagnosis(43), have a higher risk of mortality and require more resources than patients with specific complaints presenting to the ER. (42) Further, there are no universally agreed algorithms for the diagnostic workup of any of these complaints (as there is for chest pain, for example). Further details about the inclusion and exclusion criteria and the recruitment process are given in chapter 7.

4. CLINICAL INVESTIGATION OBJECTIVES

4.1 Overall Objective

The overall objective of this research project is to reveal the intended and unintended micro-, meso- and macro-level consequences by providing a DDx generator to physicians in an ER.

4.2 Primary Objective

The primary (micro-level) objective is to assess the effect of the DDx generator usage on diagnostic quality in patients admitted to the ER. Our *primary hypothesis* is that ER patients will have a slightly but significant reduced diagnostic risk when physicians are asked to consult the provided DDx generator after the first physical examination.

4.3 Secondary Objectives

Secondary objectives are

- on the micro-level, to investigate how the use of a DDx generator affects patient related outcomes such as length of stay, patient experience and satisfaction.
- on the meso-level, to understand how DDx generator affect diagnostic workflow in the ER and physicians' advice seeking, collaboration and confidence calibration.
- on the macro-level, to investigate the economic implications of DDx generators utilization in ERs and to evaluate the educational implications for physician training.

4.4 Safety Objectives

The safety objective corresponds to the primary outcome, namely how the use of a DDx generator affects diagnostic safety in patients admitted to the ER.

5. CLINICAL INVESTIGATION OUTCOMES

5.1 Primary Outcome

Primary (micro-level) endpoint is a binary score indicating a diagnostic quality risk, composed of:

- Death within 14d days after ER discharge (yes/no)
- unscheduled medical care (ER revisits, GP visits or hospitalization) within 14 days after ER discharge (yes/no)
- unexpected intensive care unit admission from ward within 24h when hospitalized (yes/no)
- diagnostic discrepancy between the ER discharge diagnosis and the current diagnosis 14 days after ER admission (yes/no)

The primary endpoint is positive, if one or multiple of the criteria above become true, and negative if none of the criteria above occur.

Justification:

There are two predominant definitions, according to which a diagnostic error is defined as “[a] failure to establish a timely and accurate diagnosis or failure to communicate it”(4) or “a diagnosis that was unintentionally delayed [...], wrong [...], or missed [...], as judged from the eventual appreciation of more definitive information”,(5) with the latter being the more commonly used definition. Consensus upon operational definition however is lacking. The variables combined in our primary endpoint were all related to diagnostic errors in previous studies and hence, may serve as indicator for the presence of a diagnostic error.(2,3,43) To assess the clinical validity of the composite endpoint, full chart reviews for a random subset of 100 patients will be performed to identify diagnostic errors / safety issues and to relate them to the variables included in our primary endpoint.(44,45)

5.2 Secondary Outcomes

Secondary outcomes include

- all variables of the primary endpoint individually
- unscheduled ER/GP revisits after 72h and 7 days
- length of ER stay
- length of hospital stay if hospitalized
- diagnostic tests in ER
- diagnostic tests after ER
- Resource consumption in ER (costs)
- Care consumption after ER discharge
- discharge destination
- patient reported outcomes
- Number and patterns of DDx provided by the physicians
- Number of cases where the generated DDx list entails the diagnoses after 14d
- Diagnostic error based on full chart review for a random subset
- CDDS usage (timing and number of queries)

5.3 Other Outcomes of Interest

Additional outcomes are physician confidence calibration, advice seeking and collaboration assessed by qualitative methods (physician observations, interviews and focus groups) to understand how DDx generator affect diagnostic workflow in the ER and physicians' advice seeking, collaboration and confidence calibration. These outcomes focus namely on physicians and their diagnostic process as a quality assurance.

5.4 Safety Outcomes

Safety outcomes correspond to the outcomes specified in the primary outcome (except diagnostic discrepancy). Additionally, serious adverse events in general will be investigated.

6. CLINICAL INVESTIGATION DESIGN

6.1 General clinical investigation design and justification of design

We will conduct an open label, cross sectional, multi-center, four-period cross-over cluster-randomized controlled superiority trial in 4 Swiss ERs.

The participating ERs will randomly be allocated to two different sequences of 2 x 2 alternating intervention and control periods of two months. During the intervention period, physicians of the respective ER will have access to the DDx generator. During the control period, the DDx generator will not be provided to the physician and the diagnostic process will follow the usual care. No wash-out periods will be applied as no substantial cross-over effects are expected given the nature of the intervention.

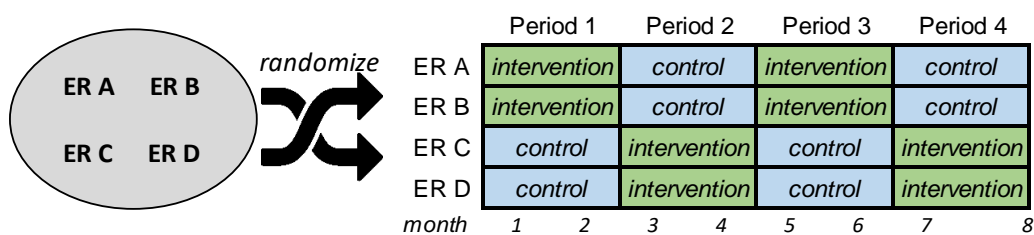


Figure 1: Study Design

Justification of the study design:

A randomized design is generally considered methodological best practice to determine the effect (causality) of an intervention.

Ideally, randomization would be conducted on the patient level. For the interventions planned in this trial however, patient level randomization is neither feasible nor advisable for several reasons: First, the intervention is primarily aimed at the ER, not the individual, because it affects the way patients are diagnosed in an ER. Second, previous studies have demonstrated the importance of staff training for the uptake of CDDS(46) and any CDDS introduction is typically followed by a phase in which staff becomes accustomed to the system and the process changes it causes before the system is fully used. Neither staff training nor a familiarization phase can be provided on a patient level. Third, many previous before-after studies have identified substantial changes to the diagnostic workup of patients after a CDDS has been introduced.(46) With randomization on a patient level, these process changes may carry over from one arm of the trial to the others, thus posing a risk of contamination. Furthermore, the attending physician may see patients with comparable symptoms form the intervention and control group in parallel (or at the same day) and be influenced by one or the other case. Therefore, there is a considerable large risk of contamination bias induced by resident-attending diagnostic workup.

A cluster-randomized design, where each participating ER is randomly assigned to conduct one of the interventions, circumvents these problems and allows for staff training and a familiarization period before patient enrolment. Last, the design eliminates the risk of contamination and allows for better adherence monitoring.

However, a cluster randomized design is susceptible to be biased by pre-existing differences between the clusters independent of the intervention. This is particularly true with a small number of clusters. To counteract the effect that pre-existing differences between the participating ERs might have on the primary outcome, we chose a cluster randomized cross-over design, where each ER is assigned a random order of periods, in which the different interventions are conducted. In effect, each participating ER will enrol patients into each trial arm. Allocation of patients to intervention groups will result from when they present to the ER and which randomly assigned period this ER is currently in.

6.2 Methods for minimising bias

6.2.1 Randomisation

There will be two pre-defined sequences with 2 x 2 alternating intervention and control periods.

6.2.2 Participating ERs will be randomly assigned to one of the two sequences prior to the recruitment phase, stratified by center size (Insel, Solothurn, vs. Tiefenau, Münsingen). An independent per-son will draw one study site from box 1 (Insel, Solothurn) and one study side from box 2 (Tiefenau, Münsingen) to allocate them to sequence 1 Intervention-Control-Intervention-Control. The remaining sites will be allocated to sequence 2 Control – Intervention – Control –Intervention Blinding procedures

Treating physicians cannot be blinded towards the patients study allocation. However, patients will be blinded, i.e. they will not be informed about the current condition (intervention or control period) of the respective ER site. The study nurses conducting the follow up interviews with patients and their general practitioners will be blinded and all raters involved in the study will be blinded (when determining whether a diagnostic discrepancy occurred and when conducting chart review to validate the measure of our primary outcome).

6.2.3 Other methods for minimising bias

n.a

6.3 Unblinding Procedures (Code break)

n.a

7. CLINICAL INVESTIGATION POPULATION

7.1 Eligibility criteria

Subjects fulfilling all of the following inclusion criteria are eligible for the investigation:

- Informed Consent signed by the subject
- Presentation to the ER with fever, abdominal pain, syncope or Non-specific complaint (NSC) as chief complaint because all these complaints occur frequently, can result from a large number of underlying diseases and thus provide room for diagnostic error. Further, there are no universally agreed algorithms for the diagnostic workup of any of these symptoms (as there is for chest pain, for example). NSC are defined as all chief complaints not included in the check list of specific complaints according to Nemec et al. 2010 (47) or as degraded general condition (german: "reduzierter Allgemeinzustand", "AZ-Reduktion" oder ähnlich) as chief complaint.
- Triage as "not vitally threatened" because study intervention would not be feasible in many cases.
- The study subject is 18 years old or older.

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Trauma as chief complaint, because there are standardized diagnostic workups, most trauma patients receive radiographic imaging and the potential benefit of a DDx generator is questionable.
- Pregnancy (anamnestic), because options for diagnostic workup are severely constrained in these patients, and presentation is mostly related to pregnancy and its complications, reducing room for error to occur and be remediated.
- Worsening of a known pre-existing condition or medical referral with a definite diagnosis, because the diagnosis is clear in this case
- Inability to follow the informed consent and investigation procedures, e.g due to language barriers, psychological disorder, admittance via police, detainee status.
- Previous enrolment into the current investigation

7.2 Recruitment and screening

Enrolment Period

Patients who present to one of the ER (Bern, Tiefenau, Solothurn, Münsingen) during the study period from June 2022 to June 2023 will consecutively be enrolled. Screening and recruitment are limited to study nurse availability. In order to achieve a balanced sample between intervention and control periods and participating sites (according to chapter 11.2), patient enrolment will be centrally monitored and study nurse availability adapted if necessary. Patients will be enrolled from week 18 (2022) to week 3 (2023) during the intervention or control phases as displayed in

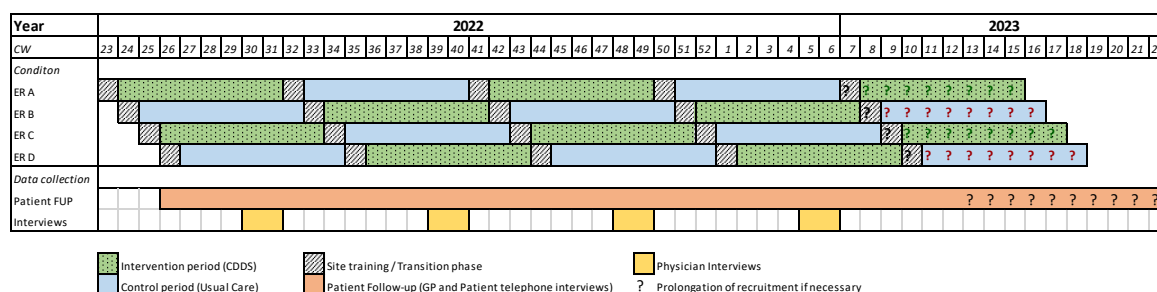


Figure 2. There will be a one-week transition phase between control and intervention phases without patient enrolment in order to accommodate sites to the new study condition and to train physicians in CDDS usage prior to the intervention phase. Recruitment will be continued at each study site until end of the enrolment period even if the targeted sample size of the respective site has been reached before. This will allow us to 1) compensate for sites that will potentially not reach the targeted sample size and 2) ensure equal length of periods. Given the nature of the cluster randomised control trial, the achieved sample size may therefore theoretically exceed the targeted sample size at end of the trial. Depending on participant recruitment and sample

size achieved, the recruitment period may be extended until week 18 in 2023 through the addition of another intervention period or control period at each site, depending on the allocated sequence of the site. Necessity and length of the additional period will be determined in week 2 of 2023, depending on recruitment achieved by then. This optional study extension allows for achievement of adequate power as determined by the sample size calculation, see section 11.2

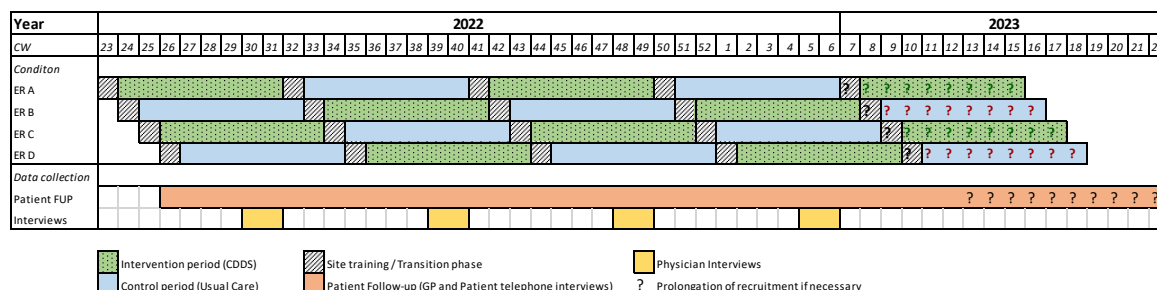


Figure 2: Study Period

Screening

Patients presenting to the ER will be registered in the ER workflow management software and triaged by hospital staff according to clinical routine. A dedicated and trained study nurses will consecutively screen the ER workflow management software for eligible study patients during his or her presence.

Recruitment

A designated study nurse explains to each subject the nature of the investigation, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject is informed that the participation in the investigation is voluntary and that he/she may withdraw from the investigation at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The subjects are informed that authorised individuals other than their treating physician may examine his/her medical records.

The subjects are informed that he/she can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their participation in the investigation. The study takes place in an emergency setting, however, only patient triaged as “non-vitally threatened” are eligible. The waiting time from admittance to first examination by a physician in non-vitally threatened patients takes usually >1 hour, depending on ER crowding. The informed consent procedure takes place within this timeframe, providing enough time to elucidate the will of the subject without leading to a delay in patient care. The inclusion period can be extended to up to 1 hour after the patient left the waiting area into the treatment area of the ER.

All subjects are given a subject information sheet and a consent form describing the investigation and providing sufficient information for the subjects to make an informed decision about their participation in the investigation. The formal consent of a subject, using the approved consent form, is obtained before the subject is submitted to any investigation procedure.

The subject should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the subject and the PI (or her/his designee). The signed consent form is retained as part of the investigation records.

The number of approached patients who either refuse to participate in the trial or are not deemed suitable for participation by the designated study nurses will be documented. In the latter case, the reason will be specified in line with the requirements for the CONSORT flow diagram. Time of informed consent or withdrawal will be documented as well.

7.3 Assignment to investigation groups

All included study patients will be allocated automatically to the investigation group of the respective site at the respective period. The random site allocation to the sequences of intervention and control period will be performed a priori as described in section 6.2.1.

7.4 Criteria for withdrawal / discontinuation of subjects

The following withdrawal criteria will apply:

- The subject's behaviour interferes with a safe conduct of the study
- Decision by the treating clinical team that termination is in the subject's best medical interest
- Decision by the Sponsor-investigator that termination is in the subjects' best medical interest
- The subject wishes to terminate the study

Data of participants who withhold consent during the trial will continue to be used in coded form and cannot be anonymized, as indicated in the Informed Consent document. No further data collection will be performed as described in chapter 9.2.5. This approach is justified, because there is a considerable risk that patients who are initially misdiagnosed and subsequently have to revisit the ER are more likely to withdraw from the study, potentially leading to an underestimation in the prevalence of the studies primary outcome.

8. CLINICAL INVESTIGATION INTERVENTION

8.1 Identity of the medical device under investigation

8.1.1 Experimental Intervention (medical device)

The medical device software under investigation is the CDDS “Isabel Pro - the DDx Generator” from ISABEL Healthcare Ltd. The German version will be used in the present study. Isabel Pro is developed for health professionals, i.e. the software is intended to support clinicians in broadening their differentials in the diagnostic workup. Namely, users are provided with a list of potential DDx based on patient characteristics and key symptoms entered as free text. Isabel Pro has explicitly been deemed as no medical device software by the manufacturer and is therefore not CE-marked as described in chapter 3.2. The medical device software is extensively described in the IB.

Isabel Pro is built to be integrated in electronic record system or workflow management system via API. We will build our own web-based interface as indicated in chapter 3.2 in order to 1) facilitate it's usage for physicians in their clinical workflow, 2) to track data input (time of use, entered symptoms etc.) and data output (provided DDx by Isabel) and 3) to save the tracked data automatically in our study database using the API of the study database.

This website can be accessed via link using a common internet browser. The users will have to log in with their email address and a personal password. A drop-down field for patient selection showing the study IDs of patients that were registered in the study database within the last 24 hours. Age category and sex for the respective patient will already be preselected using the information extracted from the study database via API. Otherwise, the functionality of the interface will follow Isabel's own web-interface. The text field for entering symptoms and clinical features incorporates Isabel's predictive text thesaurus allowing users an easy and fast query.

After query submission, patient characteristics (age, sex, travel history) and the entered symptoms on the list are sent to Isabel's Servervia API, which returns a list with possible DDx. Isabel's Database and algorithms used to seek for DDx are extensively described in the IB.

The provided output, i.e. a list of DDx follows the recommendations of the manufacturer. The first 10 of the DDx provided by Isabel according to degree of matching between entered symptoms and Isabel's disease database will be displayed with a scroll-down option to screen the remaining DDx provided by Isabel. “Do-not-miss” diagnosis are indicated by a red flag. Additionally, a link to the knowledge wikis MSD and up-to-date for each differential diagnosis where physicians can obtain more information to the respective diagnosis is provided. A notification will appear if Isabel Pro does not recognize one of the entered clinical terms. These functionalities are described more closely in the IB. The physicians will have the opportunity to adjust and rerun the query as often they wish. Data flow, i.e number of requests, the entered clinical features as well as the provided DDx will be tracked and send to the eCRF via API. Isabel Healthcare tracks and stores all queries on a server located in the UK. However, neither the study ID nor any patient identifying data will be sent to the Isabel server. Therefore, patients cannot be identified based on the data stored by Isabel Healthcare and the data can be considered anonymized. The self-build study web-interface is hosted by Hostfactory on a secured server in Switzerland. NO patient information is stored on this server. Only non-identifying patient data and the study ID is administered to the web interface and therefore, the data is considered coded. Patients can only be identified with the corresponding subject identification list as de-scribed in chapter 12.5. Additionally, we do not store any patient data on the server from hostfactory as the data will be deleted after the query has been performed and saved in the study data base on a secure CTU Bern server via API.

Training

Isabel recommends to enter medical terminology in order to receive the most accurate DDx. The software will be used by resident physicians who all have sufficient medical knowledge of the medical terminology. Usage of the software itself does not require extensive training. Isabel healthcare provides training videos of 3-5 minutes length and 2-3 slides with tips for usage. We will additionally provide a short German training video regarding our own interface. The most important tips will be provided on the interface itself. All residents will additionally be briefed by a designated study nurse before first usage. The briefing will last around 5-10 minutes and will be documented in the trial master file. Login credentials for the residents will be administrated by the local study nurses and documented in the trial master file.

8.1.2 Control Intervention (standard/routine/comparator)

The control group will receive treatment in accordance with local practice (usual care), i.e. the DDx generator will not be provided to the treating ER physicians during the control period.

8.1.3 Labelling and Supply (re-supply)

n.a

8.1.4 Storage Conditions

n.a

8.2 Discontinuation or modifications of the intervention

There are no predefined criteria to discontinue or modify the allocated intervention. However, compliance will be monitored and reasons for discontinuation or modification documented in the eCRF by the study nurses. Anticipated reasons for discontinuation or modification of the intervention are life-threatening worsening of the patients' health status that requires immediate attention and overcrowding in the ER that may prevent diagnosing physicians to consult the CDDS.

8.3 Compliance with clinical investigation intervention

The intervention is on the level of resident physicians, therefore, their compliance will be monitored by the local study nurses. Physicians will be informed about the patients' study inclusion and are asked to perform a first CDDS query after the initial patient assessment and latest within an hour after their first patient contact. During the intervention period, a check-up one hour after initial patient examination will be performed via eCRF by the local study nurse. The study nurse will approach and remind the resident accordingly if the CDDS has not been queried within the requested timeframe. In case, the resident physicians declines to use the CDDS for the respective patients, the study nurse will ask for the reason to document it in the eCRF.

During the control period, the CDDS will not be available in the respective ER. However, physicians may still use any commercially available DDx generator outside the study protocol if needed. Physicians are asked to report the usage of any other DDx generator outside the CIP to the study nurse who will then document its usage in the eCRF.

Working instructions will be provided to the study nurses and to the treating physicians to minimize deviations from the CIP.

8.4 Data Collection and Follow-up for withdrawn subjects

If a subject withdraws from the investigation and gives the reason(s), this/these shall be recorded. If such withdrawal is due to problems related to the MD safety or performance, the PI shall ask for the subjects' permission to follow his/her status/condition outside the investigation.

Data and material already collected before withdrawal will be evaluated as far possible according to Art. 3 Abs. b ClinO-MD. In case of withdrawal, after the evaluation the data will not be anonymised (i.e. the data remains coded).

The medical follow-up of withdrawn subjects, or of subjects that prematurely drop out from the investigation is described in chapter 9.2.5 and chapter 9.2.6.

8.5 Clinical investigation specific preventive measures

Numerous risk-reduction measures are in place.

- a. Every user of the MD software will be trained prior first usage
- b. Every user (i.e physician) of the MD software will be supervised by a trained study nurse while using the device for the first time in a trial subject. The physicians will be reminded to the intendent purpose of the MD software, namely that the MD software aims to help broadening the differential diagnoses by reminding on possible diagnoses without any claim that the list is complete or indeed contains the definite diagnoses.
- c. An interim analysis for safety outcomes will be performed after end of the second period.
- d. Isabel Healthcare and we will monitor server log files for error messages during MD software

usage.

8.6 Concomitant Interventions (treatments)

none

8.7 Medical Device Accountability

The sponsor-investigator will be notified by the manufacturer if the medical device software Isabel Pro will undergo any relevant updates. The version number and date will be documented in the trial master file.

8.8 Return, Analysis or Destruction of the Medical Device

In case of malfunction of the medical device software, physicians are asked to take screenshots from the error messages, which will then be documented by the study team. Malfunctions will be analysed by our medical informatics specialist and, if necessary, by the manufacturer. In addition, Isabel Healthcare and we will monitor server log files for error messages.

9. CLINICAL INVESTIGATION ASSESSMENTS

9.1 Clinical investigation flow chart(s) / table of clinical investigation procedures and assessments

Investigation Periods	Screening	Consent (ICF)	Treatment, Intervention Period		Follow-up
Emergency Care in the emergency room	Admittance and Triage	Waiting Time	Medical examination and treatment		discharged or hospitalized
Time	-1 to -5h	-1 to -5h	0 to 1h	1h + LOS	14d±4d
A) Enrolment					
In- /Exclusion Criteria	x				
Patient information		x			
Patient consent (ICF)		x			
B) Intervention					
CDDS application during intervention period			x	(x)	
CDDS usage monitoring by study nurses			x		
C) Assessments (CR : performed within clinical routine as appropriate)					
Demographics	x				
Chief complaint	CR				
Triage assessment	CR				
Medical history			CR		
Physical examination			CR	CR	
Vital signs			CR	CR	
Laboratory tests			CR	CR	
Other diagnostic tests			CR	CR	
CDDS input / output data collection			x	(x)	
Physician questionnaire			x	(x)	
Patient telephone interviews					x
Medical record review from ER, hospital and/or GP			x	x	x
(Serious Adverse Events, Adverse device effects)			x	x	x
Device Deficiencies			x	x	
D) Primary Outcome Score					
All-cause mortality					x
Unscheduled medical care if discharged (GP, ER revisit, hospitalization)					x
Unexpected ICU admission within 24h if hospitalized					x
Current diagnosis for presenting complaint				x	x

E) Secondary Outcomes					
Number and cost of ER diagnostic tests				x	x
Time to ER diagnosis				x	
ER differential diagnoses				x	
Physician confidence in ER diagnosis				x	
Physician collaboration				x	
Discharge type				CR	
ER LOS				CR	
Hospital LOS if hospitalized					CR
CDDS usage (number of queries)			x	(x)	
Patient reported outcomes					x
ER, Emergency room; ICU, intensive care unit; CDDS, computerized diagnostic decision support system; GP, general practitioner; LOS, length of stay; CR, clinical routine					

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

As described under chapter 5, the primary outcome is a composite score of parameters associated with diagnostic risk.

Parameter	Method
Death within 14±4 days after ER discharge	Study nurses will review the local EHR and contact the patient and GP for vital status information.
Unscheduled medical care for the same complaints within 14±4 days after ER discharge	Study nurses will contact patients by phone 14 days after discharge to collect information about follow-up medical care and diagnosis.
Unexpected IMC unit admission within 24h after ER discharge if hospitalized	Retrieved from the EHR system.
Discrepancy in ER discharge diagnosis and diagnosis 14±4 days after ER discharge	<p>ER discharge differential diagnoses will be looked up in the ER discharge letter and registered in the study database by the local study nurse.</p> <p>Study nurses will contact patients by phone 14 days after discharge to collect information about follow-up medical care. Additionally, medical records from the local hospital and the GP are reviewed. Information about the current diagnoses at follow-up will be sought from the EHR or the GP documentation (if available).</p> <p>Two physicians will independently review the ER differential diagnoses from ER discharge and day 14 and define whether there is a discrepancy based on clinical judgement. If a patient did not have any follow-up medical care, it is assumed that his or her diagnosis has not changed.</p>

9.2.2 Assessment of secondary outcomes

Parameter	Data collection
Number and type of diagnostic tests performed in the ER (and hospital if hospitalized)	Study nurses will retrieve the type and number of diagnostic tests performed during ER (and hospital) stay from the EHR. Following diagnostic tests (yes/no) will be recorded: Lab (Blood), Lab (Urine), Lab (Sputum), MRI, CT, Sonography, X-ray, other. Additionally, number of blood sample will be and consultation of specialists will be recorded.
Resource consumption during ER (and hospital if hospitalized) stay.	Resource consumption for each patient (costs of diagnostic tests, consultations, personal and material caused) will be obtained from the hospitals administrative database to assess costs caused during the ER stay and costs caused during hospital stay if hospitalized. Costs will additional be itemized according to the hospital's cost centres.
Sick leave days	Sick leave days will be converted to Swiss francs through the average labour productivity database of OECD
Physician confidence in ER diagnosis	The study nurse hand out an online questionnaire to the diagnosing resident physicians after patient discharge.
Discharge destination	Retrieved from the local workflow management system or EHR
ER LOS [h]	Retrieved from the local workflow management system or EHR
Hospital LOS if hospitalized [days]	Retrieved from the local EHR system.
CDDS usage (number of queries)	Monitored by the CDDS and stored automatically in the eCRF via API.
CDDS in- and output data	Monitored by the CDDS and stored automatically in the eCRF via API.
Patient reported outcomes	Telephone patient interviews through study nurses
Diagnostic Error	Chart review will be performed for a random sample of 50 patients with a positive primary endpoint and 50 patients with a negative primary endpoint to seek for diagnostic errors using the Revised Safer Dx Instrument according to Singh et al (2021).(44,45)

9.2.3 Assessment of other outcomes of interest

With qualitative methods, we aim to understand how the CDDS affects the diagnostic workflow, collaboration process, physician satisfaction with the tool, physician confidence in diagnosing, advice seeking behaviour and cooperation with other medical personal in general.

Observations (Step1) will be performed out of which guiding questions for a focus group will result (Step 2). Subsequent semi-structured interviews (Step 3) will be performed with individual participants with questions developed from results obtained from the focus group. Observation will be repeated in a later period to assess changes in workflow, satisfaction change etc. and if necessary, interviews will be performed again (Step 4). The qualitative part observes the physicians diagnostic process, not the patient.

9.2.4 Assessment of safety outcomes

Safety outcomes correspond to the outcomes specified in primary outcome. Additionally, rate of serious adverse events in general will be investigated.

9.2.4.1 Adverse events

The principal investigator will monitor the study for adverse events possibly related to the clinical investigation (ADE) as described in chapter 10.3. Time of onset, duration, resolution, intensity, actions to be taken and possible relation to the MD or the CIP is documented. Should a serious ADE occur, the study will be stopped, an investigation will be conducted and a findings report generated before the study is resumed. We do not expect such events.

Following up all adverse events (AE) according to the definition of chapter 10.1 would lead to a disproportionate administrative burden as adverse events such as untoward medical occurrence are usually the reason for an ER visit and often not resolved within the time-frame of ER stay. However, serious adverse events will be documented as part of the study outcomes and retrieved from medical records collected via patient interviews at 14d follow-up. In contrast to (S)ADEs, these events will not followed-up and documented until resolution, except a possible relation with the MD or CIP would be assumed by the study nurse collecting the data and confirmed by the PI.

9.2.4.2 Laboratory parameters

Laboratory parameters will only be assessed within clinical routine of the local ER. No additional sampling or examination will be performed for study reason, nor are any abnormal laboratory parameters considered as adverse events. Abnormal laboratory values are only recorded in text form, if they are entered as clinical symptom in the CDDS (e.g. "dyslipidemia").

9.2.4.3 Vital signs

Vital signs will only be assessed within clinical routine of the local ER. No additional assessment and recording of vital signs will be performed for study reason. Vital signs are only recorded in text form, if they are entered as clinical symptom in the CDDS (e.g. "fever").

9.2.5 Assessments in subjects who prematurely stop the clinical investigation

If a subject withdraws from the investigation and gives the reason(s), this/these shall be recorded. If such withdrawal is due to problems related to the MD safety or performance, the PI shall ask for the subjects' permission to follow his/her status/condition outside the investigation.

Data and material already collected will be evaluated as far possible according to Art. 3 Abs. b ClinO-MD. In case of withdrawal, after the evaluation the data will not be anonymised (i.e. the data remains coded).

9.2.6 Follow-up of the subjects after the regular termination of the clinical investigation

No follow-up after regular termination of the clinical investigation is foreseen.

9.3 Procedures at each visit

9.3.1 Screening

The screening occurs after ER admittance and triage assessment. Patients admitted to the ER will be triaged within the clinical routine by trained nurses according to the swiss triage system or the ESI Triage into one of 4 graduated urgency levels (REF). Triage level 2-4 do not require immediate attention and thus, makes patients eligible for the study (i.e. for the informed consent procedure). Within the triage process, chief complaints and demographics will be recorded in the ER workflow management system, which allows the study nurses to subsequently screen for potentially eligible study patients.

9.3.2 Consent (ICF)

Eligible study patients will be approached as soon as possible by the study nurses who will verify eligibility by assessing the in- and exclusion criteria. Eligible patients will be informed about the study as described under chapter 2.7 and 7.2. While waiting, patients will have time to read the written information sheet. The designated study nurse will approach the patients again to collect the signed ICF before the intervention, i.e. first CDDS query or one hour after first patient visit by the treating resident physician. Waiting time for patients triaged to urgency level 2-4 differs from around 20minutes to several hours.

As described in chapter 7.2, patients showing signs and symptoms indicating that they are unwilling to

participate will be excluded from the study. Patients will be excluded if the waiting time is not sufficient for the informed consent procedure.

9.3.3 Treatment intervention period

Study nurses will register the patient in the study database which will provide a unique subject identification number as described in chapter 2.8 and 12. Additionally, the patient will be marked as study patient within the local workflow management software.

The study nurses will notify the resident physician about the study inclusion with a reminder to query the CDDS if the patient is included during the intervention period. During the intervention period, the study nurse will closely monitor whether the CDDS has been queried by the resident and will remind him or her if necessary after one hour. Early use of Isabel in the diagnostic process was associated with greater number of differential diagnoses compared to late use (2.32 vs 0.89). (39) Therefore, we encourage the physicians to use Isabel within the first hour of their clinical reasoning, however, later usage (and re-usage) is acceptable as well within this CIP. Time of usage will be registered. In case, the CDDS has not been used, the physician will be asked to specify the reason.

After patient discharge/hospitalization or after resident shift change (whatever occurs first), the diagnosing resident physicians will receive a link to the online questionnaire about his or her confidence regarding the current (suspected) diagnosis (see chapter 9.2.2). The questionnaire will be handed out during the intervention as well as control period. If a physician was not able to fill out the questionnaire in a reasonable time after patient discharge due to ER crowding or other reasons the questionnaire data will be considered missing without being considered and documented as protocol deviation.

9.3.4 Follow-up

Patients who are discharged at home before follow-up will be contacted and interviewed via phone by a designated and trained study nurse. If patients report any medical care consumption, the corresponding medical institution (GP, hospital etc.) will be contacted to obtain the medical record. Time and number of (attempted) contact will be documented in the patient log. It will also be documented if no information from the GP could be obtained. If a patient could not be reached by phone, the patients' GP will be contacted instead. If the GP has not seen the patient between hospital discharge and follow-up time (14±4d), the patient will be considered lost-to-follow-up. The time frame for follow-up may exceed 14±4 days if the patient or primary care physician contacts the study nurses back at a later time. Date of last contact to GP or patients will be considered as patients' end of study. For patients who are still hospitalized or re-hospitalized at time of follow-up, the relevant data will be obtained from the EHR system.

10. SAFETY

10.1 Definition and Assessment of (Serious) Adverse Events and other safety related events

Adverse Event (AE) (Art. 2 Abs 57 MDR)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the MD.

Serious Adverse Event (SAE) (Art. 2 Abs 58 MDR)

Any adverse event that led to any of the following:

- (a) death,
- (b) serious deterioration in the health of the subject that resulted in any of the following:
 - (i) life-threatening illness or injury,
 - (ii) permanent impairment of a body structure or a body function,
 - (iii) hospitalisation or prolongation of patient hospitalisation,
 - (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
 - (v) chronic disease,
- (c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note: planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a

serious deterioration of the health status of the subject, is not considered an SAE

Device deficiency (Art. 2 Abs 59 MDR)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, of an investigational device, including malfunction, user errors and inadequate information supplied by the manufacturer.

Malfunction (ISO14155)

Failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the CIP.

Device deficiency with Serious Adverse Device Effect (SADE) potential (Art. 80 Abs 1 letter c MDR; ISO14155)

Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Adverse Device Effect (ADE) (ISO14155)

Adverse event possibly, probably or causally related to the use of an investigational device or procedures.

Serious Adverse Device Effect (SADE) (ISO14155)

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) (ISO14155)

Serious adverse device effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Causal Relationship of SAE (MDCG 2020-10/1)

A causal relationship towards the medical device or the procedure of the investigation should be rated by the PI and the Sponsor as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

10.2 Adverse events categorization

The adverse events are categorized by the local PI (or authorized designee) and the Sponsor-Investigator using the following algorithm:

Does the AE meet the seriousness criteria?

- No, it is not serious
 - Is the relationship to the device or the procedure possible, probable or causal?
 - No: non-related AE
 - Yes: ADE
- Yes, it is serious: SAE

- Is the relationship to the device or the procedure possible, probable or causal?
 - No: non-related SAE
 - Yes: SADE
- Is it anticipated (within expected type, severity and frequency of the complications)?
 - No: unanticipated SADE (USADE)
 - Yes: anticipated SADE (ASADE)

A causal relationship towards the medical device or study procedure will be rated as follows [Annex XV Chapter II Section 4.1 of Regulation (EU) 2017/745; Art. 32-33 ClinO-MD; MDCG 2020-10]:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

10.3 Documentation and reporting in Medical Device Category C clinical investigations

An (S)AE corresponding to the definition in chapter 10.1 is usually the reason for ER admittance and (and study inclusion) and by itself the reason for a SAE such as subsequent hospitalization. In order to reduce inappropriate administrative burden to both sponsor and CEC without compromising the patient's safety and the idea behind AE reporting, only (S)ADE and device deficiencies are collected, fully investigated and documented in the source document and appropriate CRF during the entire investigation period, i.e. from patient's informed consent until the last CIP-specific procedure, including a safety follow-up period.

- Documentation of ADEs (including SADEs by the local PI (or authorized designee) includes diagnosis or symptoms, start and stop dates of event, event treatment, event resolution, assessment of seriousness and causal relationship to MD and/or investigation procedure (Art. 32 ClinO-MD, ISO14155).
- Documentation of DDs by the local PI (or authorized designee) includes description of event, start date, investigational device information, action taken with regard to the investigational device, and whether the DD led to an AE. The Sponsor-Investigator shall review all DDs and determine and document in writing whether they could have led to a SAE (DD with SADE potential) (Art 32. ClinO-MD, ISO14155).
- Serious adverse events not related to the MD or CIP will be documented as part of the study outcomes and retrieved from medical records collected via patient interviews at 14d follow-up. In contrast to (S)ADEs, these events will not followed-up and documented until resolution, except a possible relation with the MD or CIP would be assumed by local PI (or designee) and confirmed by the Sponsor-Investigator.
-

The Sponsor-Investigator provides the CA and the CEC with the documentation at their request (Art. 32 ClinO-MD).

10.3.1 Foreseeable adverse events and anticipated adverse device effects

An untoward medical occurrence, disease, injury, clinical signs or a serious deterioration in health of the subject is usually the reason for ER admittance. Therefore, any of these events during ER stay or subsequent hospitalisation is foreseeable as well as expected to occur very likely. As described in chapter 3.7, no direct adverse device effects are anticipated.

10.3.2 Reporting of (Serious) Adverse Events, device deficiencies, and other safety related events

Reporting to the Sponsor-Investigator:

The following events are to be reported to the Sponsor-Investigator by the local PI (or authorized designee) within 24 hours after becoming aware of the event:

- All SAEs
- Health hazards that require measures
- Device deficiencies

The Sponsor-Investigator will evaluate SAEs with regard to causality and seriousness. Device deficiencies are also assessed regarding their potential to lead to an SAE (DD with SAE potential).

Reporting to the Competent Ethics Committee and to Swissmedic:

The following events are to be reported to the CEC and to the CA promptly (Art. 33 ClinO-MD):

- a. any serious adverse event which has a causal relation with the MD, comparator or procedure/test method or where a causal relation appears to be possible (SADE);
- b. any device deficiency which, in the absence of appropriate measures or intervention or in less favourable circumstances, could have led to serious adverse events (DD with SAE potential);
- c. any new information relating to an event already notified under points (a) and (b).

In order to ensure prompt notification, the Sponsor-Investigator may initially submit an incomplete notification.

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation, the Sponsor-Investigator notifies the CEC within 2 days of these measures and the circumstances which made them necessary (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):

An Annual Safety Report (ASR) is submitted by the Sponsor to the CEC and to the CA, yearly (Art. 35, 38 ClinO-MD). The ASR contains a list of all SAEs and DDs and a report on their degree of seriousness, causal relationship with the MD and procedure and on subjects' safety.

10.3.3 Follow-up of (Serious) Adverse Events

Ongoing (S)ADEs will be followed until resolution or until 30d after study termination. The local study team will request medical records from treating physicians (GP, hospital) or contact the patient directly by phone if necessary. Follow-up of ongoing (S)ADEs will be repeated every two month after start of the (S)ADEs until resolution and the status documented in the eCRF.

Reporting to the Competent Ethics Committee:

The Sponsor-Investigator reports to the CEC promptly any serious adverse event which has a causal relation with the MD, comparator or procedure/test method or where a causal relation appears to be possible (Art. 33 ClinO-MD).

In order to ensure prompt notification, the Sponsor may initially submit an incomplete notification.

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation, the Sponsor notifies the CEC within 2 days of these measures and the circumstances which made them necessary (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):

An Annual Safety Report (ASR) is submitted by the Sponsor to the CEC, yearly. The ASR contains a list of all SAEs and DDs and a report on their degree of seriousness, causal relationship with the MD and procedure and on subjects' safety.

Other reporting is done according to provisions of MD vigilance as per Art. 87-90 MDR (Art. 33 abs 4.b ClinO-MD) and Art. 67 MedDO.

10.4 Assessment, notification and reporting on the use of radiation sources

n.a

11. STATISTICAL METHODS

11.1 Hypothesis

The Null Hypothesis is that there is no difference in the proportion of the composite diagnostic risk score between the intervention and comparator condition. The Alternative Hypothesis is that there is a nonzero difference in the proportion of the composite diagnostic risk score between the intervention and comparator condition.

11.2 Determination of Sample Size

The sample size calculation has been performed for a multi-period cross-over cluster randomized controlled trial using according to Hemming at al. (2020) using the web-tool The Shiny CRT Calculator.(48)

The trial is designed to have a power of 80% to detect a clinically significant between-condition-difference in the primary outcome of 5 percent points on an alpha level of 0.05.

For the primary outcome, we assumed a positive composite score in 12% of the cases in the control condition. Further assumptions were a cross-sectional sampling and exchangeable correlation structure, an intra cluster correlation between 0.01 and 0.05, a coefficient of variation of cluster size of 0.5 and a 10% lost-to-follow up patients.

With 4 periods and 2 clusters (ERs) per sequence and the minimal sample size to detect a clinically significant between-condition-difference in the primary outcome of 5 percent points on an alpha level of 0.05 with a power of 80% equals to (in average) 74 patients per period and cluster and 1'184 patients in total.

The required sample size for each site is given below, proportional to the number of the overall patients treated yearly in the participating ERs:

Site	Patients per year (data from 2018)	Required Sample Size (per month)
ER Insel Bern	44'532	560 (70)
ER Tiefenau Bern	11'446	134 (17)
ER Solothurn	33'446	394 (49)
ER Münsingen	~ 8'000*	96 (12)
Total	97'424	1'184 (148)

*estimated by head physician of ER

According to data from 2020 of the lead ER Insel Bern, 877 patients with a chief complaint syncope, abdominal pain or fever presented to the ER

from May to December 2020 (Figure 3). Including all patients presenting with NSC, the number of eligible patients is well above the required sample size needed for the present study. We assume, that the proportion of eligible patients to overall patients is comparable between the participating ER sites.

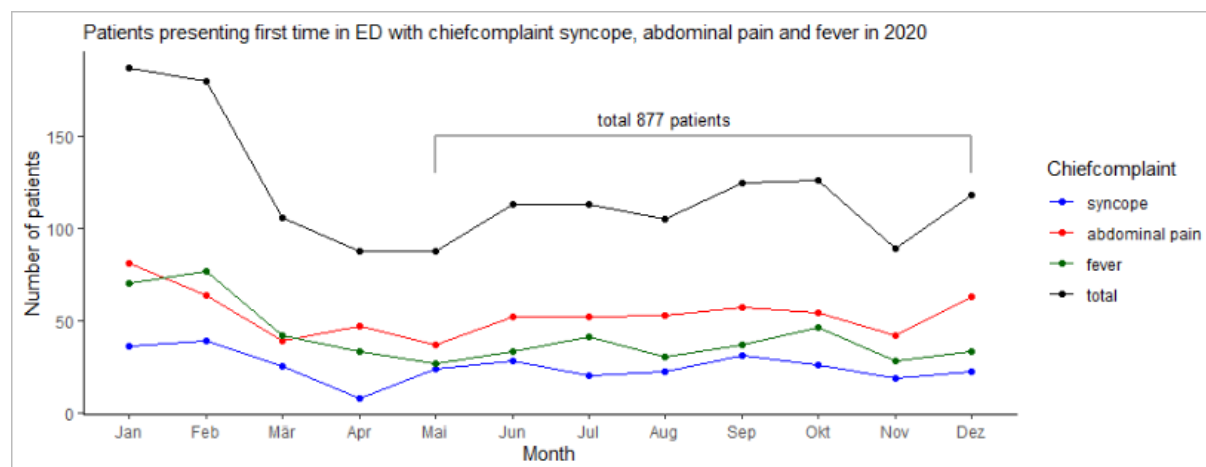


Figure 3: Patients presenting first time in ED with chief complaint syncope, abdominal pain and fever.

11.3 Statistical criteria of termination of the investigation

Statistical criteria of termination of the investigation is the inclusion of >1'232 patients and end of the 4th period.

11.4 Planned Analyses

Statistical analysis will be based on multi-level general linear mixed modelling (GLMM) methods using appropriate post hoc techniques (e.g for subgroup analyses).

Standard descriptive statistics, and illustrative graphing will be used throughout, along with normality testing (e.g. Shapiro-Wilk) in order to check assumptions for the appropriate use of parametric testing approaches. Transformations to normality for variables not fulfilling normality assumptions will be considered (e.g. log, Box-Cox etc.), while nonparametric testing using counterparts of ad-hoc parametric procedures will also be an option as needed (e.g. Kruskal-Wallis instead of one-way ANOVA, the latter being part of the GLM family). R (R Foundation for Statistical Computing, Vienna, Austria) will be used for data analysis. A test-wise 2-sided p-value of less than 0.05 (after post-hoc and/or FDR adjustment if deemed appropriate) will be considered statistically significant. All statistical analyses will be performed by the applicant's research team biostatisticians and involve statistical counselling by the Clinical Trial Unit as needed.

11.4.1 Datasets to be analysed, analysis populations

Data will be analysed according to the intention-to-treat principle. Data from all participant with or without protocol violation including dropouts and withdrawals will be included in the main analysis. A Per-Protocol (PP) analysis will be performed as sensitivity analysis. Patients from the intervention group will be removed from the PP-analysis if no CDDS query has been documented. Vice versa, patients from the control group will be removed from the analysis if physicians self-report the query of any DDx generator outside the study protocol.

11.4.2 Primary Analysis

For the primary outcome (presence or no presence of a positive diagnostic quality risk score), a generalized linear mixed model (GLMM) with a binomial distribution family and exchangeable correlation structure will be performed. The GLMM takes into account a random effect for each site, resident and attending physician. Diagnosing resident and attending physicians are nested within sites. The condition (intervention and control) and the period (period 1 to 4) will be included as fixed factors under the

assumption of equality of carry-over effects. Additionally, presenting chief complaint, patient's age, sex and comorbidity index will be added as covariates.

11.4.3 Secondary Analyses

For all secondary endpoints, summary statistics appropriate to the distribution will be tabulated by treatment group. Analysis of secondary endpoints will parallel the primary analysis.

11.4.4 Interim analyses

An interim analysis for safety outcomes is planned after the end of the second period. Based on their evaluations, it will be decided by the sponsor-investigator and the site PIs if premature stopping of the clinical investigation is required.

11.4.5 Deviation(s) from the original statistical plan

Deviations from the original statistical plan will be described and justified in the final report.

11.1 Handling of missing data and drop-outs

Missing data will be imputed by multiple imputation. Lost-to-follow-up patients will be contacted three times. If a trial subject can no longer be traced, its address and state of health will be clarified by the investigator with the contact person. Drop outs will not be replaced. All subjects shall be accounted for and documented, including those withdrawn from the investigation or lost to follow-up. Sensitivity analyses on the effect of the missing data on results will be performed.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

All study data will be collected and archived in a coded format in the study database with the exception of signed informed consent forms which will be stored in a locked cabinet.

12.1.1 Case Report Forms

Data will be recorded using electronic Case Report Forms (eCRFs). During the study, eCRFs will be kept up to date by the study team. The study delegation log describes who will be authorized for eCRF entries. Once data collection is completed and validated, the local PI will sign off all eCRFs.

CRFs are linked with participants' study ID. Each study participant will be assigned a study ID consisting of a four-digit number of the site and an ascending number of the included patient for the respective site (e.g. 2899-1, 2899-2, 2899-3 ...). All collected data will be coded accordingly. The subject identification list will be kept in the Investigator Site File during the course of the clinical trial. After completion or termination of the study, the subject identification list will be kept by a person outside of the study team (Directorate Teaching and Research, Insel Gruppe)). In case of further use of research data, the researchers in charge will not have access to the subject identification list.

12.1.2 Specification of source data and source documents

The data management plan specifies what constitutes source data. In case CRFs are not serving as source documents, source documents will be retained for audit trail purposes. Location of source data is agreed in the data management plan.

Source data contain signed Informed Consent Forms, data retrieved from the local electronic health record system, in- and output of the CDDS sent directly to the eCRF via API, all clinical and safety related data that is directly recorded in the eCRF (follow-up medical care for presenting complaints reported by patients) and medical record from the treating GP.

12.1.3 Archiving of essential clinical investigation documents

All the documents of the investigation will be archived for a minimum of 10 years after regular or premature termination of the investigation. Electronic data will be archived within the study database and paper-based documents (signed informed consent forms) in the local ER departments.

12.2 Data management

12.2.1 Data Management System

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system (REDCap). The EDC system is activated for the trial only after successfully passing a formal test procedure. All data entered in the CRFs are stored on a Linux server in a dedicated MySQL database. Responsibility for hosting the EDC system and the database lies with CTU Bern.

Designated investigator staff will enter the data required by the protocol into the eCRF. CDDS in- and output will be sent automatically from the CDDS into the REDCap eCRF database using an API.

12.2.2 Data security, access and back-up

The server hosting of the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server and back-up tapes. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.

All data entered into the CRFs are transferred to the database using Secure Sockets Layer encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail).

A multi-level back-up system is implemented. Back-ups of the whole system including the database are run internally several times per day and on external tapes once a day. The back-up tapes are stored in a secure place in a different building status of the database at this time is recorded in special archive tables. CTU Bern will securely store the final study database with all archive tables for at least 15 years.

12.2.3 Analysis and archiving

The study database with all archive tables will be securely stored by CTU Bern for at least 15 years. The sponsor also keeps the Trial Master File and final reports for at least 10 years.

At final analyses, data files will be extracted from the database into statistical packages to be analyzed. The status of the database at this time is recorded in special archive tables.

The extracted coded datafiles will be stored on a SharePoint 2013 platform that was centrally set up by the University Hospital Bern. It fulfils all requirements of the Human Research Act (HRA). The physical location of the servers is in Zollikofen BE.

The SharePoint server is kept in a locked server-room. Only the system administrators have direct access to the server and back-up tapes. Each access on the platform occurs only with personal credentials (user name and password). The credentials are managed centrally in the Active Directory System of the Inselspital. An anonymous access to the SharePoint platform is not possible. A role concept (read, read/write and administrator) is realised using SharePoint groups and regulates permission for each user and each research project in order to use the system as he/she requires. Every access to the SharePoint server is recorded by the audit function of the SharePoint Server. This audit trail contains information about the accessing user, date and time of access and the name of the document that was accessed. The tracking of the actual data changes is not included in this audit trail. Therefore, the SharePoint versioning functionality is at all times switched on. The comparison of different versions of research document (using the Excel Inquire add-on of Microsoft Excel 2013) ensures the traceability of data changes. The backup of the server and the database instances is done once a week by 1 full and 6 incremental backups. The retention time is 30 days.

The research data files on the SharePoint platform will remain available to all authorised participants for at least 10 years.

12.2.4 Electronic and central data validation

Data is checked by the EDC system for completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant. In addition, central data reviews will be performed on a regular basis to ensure completeness of the data collected and accuracy of the primary outcome data.

12.3 Monitoring

Monitoring will be provided by a study nurse not involved in the study. Study data will be centrally

monitored by a study nurse (Department of Neurosurgery, Inselspital, Bern University Hospital, University of Bern)), who is not involved in the recruitment, randomization, or assessment of the data. Monitoring will follow the recommended monitoring strategies for mid-risk trials according to the Guidelines for risk-based monitoring (version 2.0) from the swiss clinical trial organisation. Monitoring visits consists of a pre-trial visit, site initiation visit, a routine monitoring visit after the inclusion of the first trial subject and 2-3 routine monitoring visit dependent of recruitment and a closeout visit at the end of the recruitment period. The monitor will check the informed consent of 100% of trial subjects and will perform 100% source data verification for the first three trial subject and additional 10% of randomly selected trial subjects. Source data verification will be performed for eligibility, primary endpoint (except diagnostic discrepancy as this will determined after study end) and SADEs for 35% of all subjects. Trial master file and site investigation file will be checked at the beginning and the end of the study. Completeness of the authorisation, screening, identification and enrolment list as well as training documentation will be checked on a regular basis during the routine monitoring visits. Frequency and Intensity of monitoring will be increased if data quality decreases or large changes in team or protocol occur as specified in the monitoring plan.

Source data and documents will be accessible to monitors and questions are answered during monitoring by the PI and the site staff.

12.4 Audits and Inspections

No specific audits or inspections are planned. However, the study documentation and the source data/documents will be accessible to potential auditors/inspectors (CEC and CA) and questions will be answered during inspections. All involved parties will have to be kept the participant data strictly confidential.

12.5 Confidentiality, Data Protection

Each study participant will be assigned a study ID consisting of a four-digit number of the site and an ascending number of the included patient for the respective site (e.g 2899-1, 2899-2, 2899-3 ...). (see section 12.5 Confidentiality, Data Protection).

All collected data will be coded accordingly. The subject identification list will be kept in the Investigator Site File during the course of the clinical trial. After completion or termination of the study, the subject identification list will be kept by a person outside of the study team (Directorate Teaching and Research, Insel Gruppe) In case of further use of research data, the researchers in charge will not have access to the subject identification list.

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections. The local investigation personnel will have access to the respective local investigation documents during and after the investigation. The sponsor-investigator and the project leaders will have access to the coded dataset during and after the investigation. In agreement with the sponsor-investigator, minimal coded datasets may be distributed for statistical analysis (e.g to a statistician) or published if requested by scientific journals as described in chapter 13.

12.6 Storage of biological material and related health data

No biological material will be collected during the study. Health-related data will be stored in study database for a minimum of 10 years as outlined above.

13. PUBLICATION AND DISSEMINATION POLICY

Insights provided by this study will be disseminated to scientists, health care professionals, study participants, patient societies, industry and policymakers. Data will be submitted for publication in internationally peer-reviewed scientific journals. The privacy of each subject and confidentiality of their information shall be preserved in reports and publication of data. Minimal coded subject-level datasets and statistical codes may be published online if requested by scientific journals. It will be published in the final study report whether gender effects are observed or not.

This study is designed as a multicentre trial. All participating sites and sponsor agree that the first and all major publications from this study shall be joint publications. A major publication is defined as any publication that presents data obtained at more than a single site.

The PIs from each site that contributed data used in a publication and all persons named in chapter 1.8 committee will be invited to contribute to these publications. Two additional authorship for the person suggesting a publication and leading its write-up may be offered.

Individuals must fulfil ICMJE authorship criteria in order to be considered as an author on any given publication (www.icmje.org/#author). According to these requirements, authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

The privacy of each subject and confidentiality of their information shall be preserved in reports and publication of data. Minimal coded subject-level datasets and statistical codes may be published online if requested by scientific journals.

14. FUNDING AND SUPPORT

14.1 Funding

The study is funded by the Swiss National Science Foundation under contract number 407740_187284/1.

14.2 Other Support

15. N.AINSURANCE

Study insurance will be provided by the University Hospital of Bern. A copy of the certificate will be filed in the investigator site file and the trial master file.

16. REFERENCES

1. Declaration of Helsinki, Version October 2013 (<http://www.wma.net/en/30publications/10policies/b3/index.html>)
 2. Humanforschungsgesetz, HFG Bundesgesetz über die Forschung am Menschen (Bundesgesetz über die Forschung am Menschen, HFG) vom 30. September 2011/ Loi fédérale relative à la recherche sur l'être humain (loi relative à la recherche sur l'être humain, LRH) du 30 septembre 2011 / Legge federale concernente la ricerca sull'essere umano (Legge sulla ricerca umana, LRUm) del 30 settembre 2011
 3. Verordnung über klinische Versuche mit Medizinprodukten (KlinV-Mep) vom 1. Juli 2020 / Ordonnance sur les essais cliniques de dispositifs médicaux (OClin-Dim) du 1er juillet 2020 /. Ordinanza sulle sperimentazioni cliniche con dispositivi medici (OSRUm-Dmed) del 1 luglio 2020
 4. Verordnung über klinische Versuche in der Humanforschung (Verordnung über klinische Versuche, KlinV) vom 20. September 2013 / Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain (Ordonnance sur les essais cliniques, OClin) du 20 septembre 2013. Ordinanza sulle sperimentazioni cliniche nella ricerca umana (Ordinanza sulle sperimentazioni cliniche, OSRUm) del 20 settembre 2013
 5. Medizinprodukteverordnung (MepV) vom 17. Oktober 2001 / Ordonnance sur les dispositifs médicaux (ODim) du 17 octobre 2001 / Ordinanza relativa ai dispositivi medici (ODmed) del 17 ottobre 2001
 6. Medical Device Regulation (EU) 2017/745 of 5 April 2017 (MDR) (<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745>)
 7. MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 (https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-1_guidance_safety_reporting_en.pdf)
 8. EN ISO 14155: Clinical investigation of medical devices for human subjects - Good clinical practice (www.iso.org)
 9. EN ISO 10993: Biological evaluation of medical devices (www.iso.org)
 10. EN ISO 14971: Application of risk management to medical devices (www.iso.org)
 11. International Conference on Harmonization (ICH) Guideline for Good Clinical Practice E6(R2). (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf)
-
1. Berner ES, Graber ML. Overconfidence as a cause of diagnostic error in medicine. Am J Med. Mai 2008;121(5 Suppl):S2-23.
 2. Hautz WE, Kämmer JE, Hautz SC, Sauter TC, Zwaan L, Exadaktylos AK, u. a. Diagnostic error increases mortality and length of hospital stay in patients presenting through the emergency room. Scand J Trauma Resusc Emerg Med. 8. Mai 2019;27(1):54.
 3. Singh H, Meyer AND, Thomas EJ. The frequency of diagnostic errors in outpatient care: estimations from three large observational studies involving US adult populations. BMJ Qual Saf. September 2014;23(9):727–31.
 4. Committee on Diagnostic Error in Health Care, Board on Health Care Services, Institute of Medicine, The National Academies of Sciences, Engineering, and Medicine. Improving Diagnosis in Health Care [Internet]. Balogh EP, Miller BT, Ball JR, Herausgeber. Washington, D.C.: National Academies Press; 2015 [zitiert 28. April 2017]. Verfügbar unter: <http://www.nap.edu/catalog/21794>
 5. Graber ML, Franklin N, Gordon R. Diagnostic Error in Internal Medicine. Arch Intern Med. 11. Juli 2005;165(13):1493.
 6. Newman-Toker DE. Diagnostic Errors—The Next Frontier for Patient Safety. JAMA. 11. März 2009;301(10):1060.
 7. Kachalia A, Gandhi TK, Puopolo AL, Yoon C, Thomas EJ, Griffey R, u. a. Missed and delayed diagnoses in the emergency department: a study of closed malpractice claims from 4 liability insurers. Ann Emerg Med. Februar 2007;49(2):196–205.

8. Schaffer AC, Jena AB, Seabury SA, Singh H, Chalasani V, Kachalia A. Rates and Characteristics of Paid Malpractice Claims Among US Physicians by Specialty, 1992-2014. *JAMA Intern Med.* 1. Mai 2017;177(5):710.
9. Weeks WB, Foster T, Wallace AE, Stalhandske E. Tort Claims Analysis in the Veterans Health Administration for Quality Improvement. *J Law Med Ethics.* September 2001;29(3–4):335–45.
10. Croskerry P. The importance of cognitive errors in diagnosis and strategies to minimize them. *Acad Med.* 2003;78(8):775–80.
11. Norman GR, Monteiro SD, Sherbino J, Ilgen JS, Schmidt HG, Mamede S. The Causes of Errors in Clinical Reasoning: Cognitive Biases, Knowledge Deficits, and Dual Process Thinking. *Acad Med.* Januar 2017;92(1):23–30.
12. Zwaan L, de Bruijne M, Wagner C, Thijs A, Smits M, van der Wal G, u. a. Patient record review of the incidence, consequences, and causes of diagnostic adverse events. *Arch Intern Med.* 28. Juni 2010;170(12):1015–21.
13. Zwaan L, Thijs A, Wagner C, van der Wal G, Timmermans DRM. Relating Faults in Diagnostic Reasoning With Diagnostic Errors and Patient Harm: *Acad Med.* Februar 2012;87(2):149–56.
14. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. *NPJ Digit Med.* 2020;3:17.
15. Patterson BW, Pulia MS, Ravi S, Hoonakker PLT, Schoofs Hundt A, Wiegmann D, u. a. Scope and Influence of Electronic Health Record–Integrated Clinical Decision Support in the Emergency Department: A Systematic Review. *Ann Emerg Med [Internet].* Januar 2019 [zitiert 1. Februar 2019]; Verfügbar unter: <https://linkinghub.elsevier.com/retrieve/pii/S0196064418314227>
16. Jain B. The key role of differential diagnosis in diagnosis. *Diagnosis.* 27. November 2017;4(4):239–40.
17. Kostopoulou O. Diagnosis of Difficult Cases in Primary Care. *J Health Serv Res Policy.* Januar 2010;15(1_suppl):71–4.
18. Kostopoulou O, Devereaux-Walsh C, Delaney BC. Missing Celiac Disease in Family Medicine: The Importance of Hypothesis Generation. *Med Decis Making.* Mai 2009;29(3):282–90.
19. Singh H, Giardina TD, Meyer AND, Forjuoh SN, Reis MD, Thomas EJ. Types and Origins of Diagnostic Errors in Primary Care Settings. *JAMA Intern Med.* 25. März 2013;173(6):418.
20. Ely JW, Kaldjian LC, D'Alessandro DM. Diagnostic Errors in Primary Care: Lessons Learned. *J Am Board Fam Med.* 1. Januar 2012;25(1):87–97.
21. Pelaccia T, Tardif J, Triby E, Ammirati C, Bertrand C, Dory V, u. a. How and when do expert emergency physicians generate and evaluate diagnostic hypotheses? A qualitative study using head-mounted video cued-recall interviews. *Ann Emerg Med.* Dezember 2014;64(6):575–85.
22. Neurath PW, Enslein K, Mitchell GW. Design of a Computer System to Assist in Differential Preoperative Diagnosis for Pelvic Surgery. *N Engl J Med.* 3. April 1969;280(14):745–9.
23. Riches N, Panagioti M, Alam R, Cheraghi-Sohi S, Campbell S, Esmail A, u. a. The Effectiveness of Electronic Differential Diagnoses (DDX) Generators: A Systematic Review and Meta-Analysis. Schmidt RL, Herausgeber. *PLOS ONE.* 8. März 2016;11(3):e0148991.
24. Hautz WE, Kammer JE, Schaubert SK, Spies CD, Gaissmaier W. Diagnostic performance by medical students working individually or in teams. *JAMA.* 20. Januar 2015;313(3):303–4.
25. Kämmer JE, Hautz WE, Herzog SM, Kunina-Habenicht O, Kurvers RHJM. The Potential of Collective Intelligence in Emergency Medicine: Pooling Medical Students' Independent Decisions

Improves Diagnostic Performance. *Med Decis Making*. 29. März 2017;37(6):715–24.

26. Semigran HL, Linder JA, Gidengil C, Mehrotra A. Evaluation of symptom checkers for self diagnosis and triage: audit study. *BMJ*. 8. Juli 2015;h3480.
27. Kanagasingam Y, Xiao D, Vignarajan J, Preetham A, Tay-Kearney M-L, Mehrotra A. Evaluation of Artificial Intelligence–Based Grading of Diabetic Retinopathy in Primary Care. *JAMA Netw Open*. 28. September 2018;1(5):e182665.
28. Apkon M. A Randomized Outpatient Trial of a Decision-Support Information Technology Tool. *Arch Intern Med*. 14. November 2005;165(20):2388.
29. Ramnarayan P, Tomlinson A, Rao A, Coren M, Winrow A, Britto J. ISABEL: a web-based differential diagnostic aid for paediatrics: results from an initial performance evaluation. *Arch Child*. Mai 2003;88(5):408–13.
30. Bavdekar SB, Pawar M. Evaluation of an Internet delivered pediatric diagnosis support system (ISABEL) in a tertiary care center in India. *Indian Pediatr*. November 2005;42(11):1086–91.
31. Ramnarayan P, Cronje N, Brown R, Negus R, Coode B, Moss P, u. a. Validation of a diagnostic reminder system in emergency medicine: a multi-centre study. *Emerg Med J*. September 2007;24(9):619–24.
32. Graber ML, Mathew A. Performance of a web-based clinical diagnosis support system for internists. *J Gen Intern Med*. 2008/01/10 Aufl. Januar 2008;23 Suppl 1(Suppl 1):37–40.
33. Bond WF, Schwartz LM, Weaver KR, Levick D, Giuliano M, Graber ML. Differential diagnosis generators: an evaluation of currently available computer programs. *J Gen Intern Med*. 2011/07/27 Aufl. Februar 2012;27(2):213–9.
34. Riches N, Panagioti M, Alam R, Cheraghi-Sohi S, Campbell S, Esmail A, u. a. The Effectiveness of Electronic Differential Diagnoses (DDX) Generators: A Systematic Review and Meta-Analysis. *PLoS One*. 2016;11(3):e0148991.
35. Ramnarayan P, Roberts GC, Coren M, Nanduri V, Tomlinson A, Taylor PM, u. a. Assessment of the potential impact of a reminder system on the reduction of diagnostic errors: a quasi-experimental study. *BMC Med Inform Decis Mak*. 28. April 2006;6:22.
36. Graber ML, Tompkins D, Holland JJ. Resources medical students use to derive a differential diagnosis. *Med Teach*. Juni 2009;31(6):522–7.
37. Carlson J, Abel M, Bridges D, Tomkowiak J. The impact of a diagnostic reminder system on student clinical reasoning during simulated case studies. *Simul Healthc J Soc Simul Healthc*. Februar 2011;6(1):11–7.
38. Thomas NJ, Ramnarayan P, Bell MJ, Maheshwari P, Wilson S, Nazarian EB, u. a. An international assessment of a web-based diagnostic tool in critically ill children. *Technol Health Care Off J Eur Soc Eng Med*. 2008;16(2):103–10.
39. Sibbald M, Monteiro S, Sherbino J, LoGiudice A, Friedman C, Norman G. Should electronic differential diagnosis support be used early or late in the diagnostic process? A multicentre experimental study of Isabel. *BMJ Qual Saf*. 5. Oktober 2021;bmjqs-2021-013493.
40. Kämmer JE, Schaubert SK, Hautz SC, Stroben F, Hautz WE. Differential diagnosis checklists reduce diagnostic error differentially: a randomized experiment. *Med Educ*. 21. Juli 2021;medu.14596.
41. Zwaan L, Singh H. Diagnostic error in hospitals: finding forests not just the big trees. *BMJ Qual Saf*. Dezember 2020;29(12):961–4.
42. Kemp K, Mertanen R, Lääperi M, Niemi-Murola L, Lehtonen L, Castren M. Nonspecific complaints

in the emergency department – a systematic review. Scand J Trauma Resusc Emerg Med. Dezember 2020;28(1):6.

43. Sauter TC, Capaldo G, Hoffmann M, Birrenbach T, Hautz SC, Kämmer JE, u. a. Non-specific complaints at emergency department presentation result in unclear diagnoses and lengthened hospitalization: a prospective observational study. Scand J Trauma Resusc Emerg Med [Internet]. Dezember 2018 [zitiert 30. Juli 2018];26(1). Verfügbar unter: <https://sjtrem.biomedcentral.com/articles/10.1186/s13049-018-0526-x>
44. Singh H, Bradford A, Goeschel C. Operational measurement of diagnostic safety: state of the science. Diagnosis. 23. Februar 2021;8(1):51–65.
45. Singh H, Khanna A, Spitzmueller C, Meyer AND. Recommendations for using the Revised Safer Dx Instrument to help measure and improve diagnostic safety. Diagnosis. 26. November 2019;6(4):315–23.
46. Castillo RS, Kelemen A. Considerations for a Successful Clinical Decision Support System: CIN Comput Inform Nurs. Juli 2013;31(7):319–26.
47. Nemec M, Koller MT, Nickel CH, Maile S, Winterhalder C, Karrer C, u. a. Patients Presenting to the Emergency Department With Non-specific Complaints: The Basel Non-specific Complaints (BANC) Study. Acad Emerg Med. März 2010;17(3):284–92.
48. Hemming K, Kasza J, Hooper R, Forbes A, Taljaard M. A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator. Int J Epidemiol. 1. Juni 2020;49(3):979–95.

17. APPENDICES

Documents provided separately:

1. Investigator's Brochure
2. General Insurance Conditions, insurance certificate
3. Case Report Form (ISO14155 Annex C)
4. Monitoring Plan