Impact of a diagnostic algorithm

including clinically guided point-of-care C-reactive protein testing and safety netting advice on antibiotic prescribing rate and further management of

acutely ill children presenting to ambulatory care:

multicentre, cluster-randomized, parallel group pragmatic trial

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TITLE PAGE

FULL/LONG TITLE OF THE TRIAL

Impact of a diagnostic algorithm including clinically guided point-of-care C-reactive protein testing and safety netting advice on antibiotic prescribing rate and further management of acutely ill children presenting to ambulatory care: multicentre, cluster-randomized, parallel group pragmatic trial

SHORT STUDY TITLE / ACRONYM

Impact of clinical guidance & point-of-care CRP in children: the ARON project

PROTOCOL VERSION NUMBER AND DATE

Protocol version 3.0 date 28/04/2023

RESEARCH REFERENCE NUMBERS

EudraCT Number:	Not applicable
Clinical trials.gov Number / Other registry Number:	this trial will be registered at clinicaltrials.gov
SPONSOR Number:	s62005
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TABLE OF CONTENTS

SIGNATURE PAGE

Only the final version(s) need to be signed

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

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

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

For and on behalf of the Study Sponsor, Chief Investigator:		
Signature:		Date: ...../...../.....
Name: (please print): Prof Dr Jan Y Verbakel		
Statistician:		
Signature:		Date: ...../...../.....
Name: (please print): Ms Annouschka Laenen		
Position: Biostatistician, Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat)		
For acknowledgement on behalf of the funder (KCE):		
Signature:		Date: ...../...../.....
Name (please print):		
Position:		

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TRIAL SUMMARY

Trial Title	Impact of a diagnostic algorithm including clinically guided point-of-care C-reactive protein (CRP) testing and safety netting advice on antibiotic prescribing rate and further management of acutely ill children presenting to ambulatory care: multicentre, cluster-randomized, parallel group pragmatic trial
Short title	Impact of clinical guidance & point-of-care CRP test in children: the ARON project
Trial Design	multicentre, cluster-randomized, parallel group pragmatic trial
Trial Participants and setting	Children aged 6 months to 12 years of age with an acute illness episode presenting to in-hours general practice or out-of-hospital community paediatrics offices
Intervention(s)	Diagnostic algorithm (see Flowchart, Figure 2): 1. Clinical decision tree: clinician's gut feeling something is wrong, dyspnea, temperature ≥40°C 2. **YES to any** → point-of-care CRP ≥5mg/L: **additional testing** or **refer** to secondary care <5mg/L: **safety netting***, **only** prescribe antibiotics if advised (guidelines) 3. **NO to all** → are AB considered? **YES** → point-of-care CRP ≥5mg/L: **safety netting***, **only** prescribe antibiotics if advised (guidelines) <5mg/L: **safety netting***, **do not** prescribe antibiotics **NO: safety netting** ***safety netting advice**: o inform parents on what to expect and what to look out for o interactive parent information booklet based on previous research
Control	Diagnosis and Treatment/Management as **per usual care** (see Figure 3): - **guidance on AB prescribing:**

	○ Belgische Commissie voor de Coördinatie van het Antibioticabeleid (BAPCOC) guide (updated November 2019) ○ RIZIV consensus meeting report "Antibiotics in children in ambulatory care"
Primary Endpoint	Antibiotic prescribing rate at index consultation
Secondary Endpoint(s)	- time until full clinical recovery (during follow up (day 1 to day 30)) - additional investigations (at index consultation and/or during follow up (day 1 to day 30)) - re-consultation (during follow up (day 1 to day 30)) - antibiotic prescribing rate (during follow up (day 1 to day 30))
Exploratory endpoints	At the **index** consultation: - additional investigations (X-Ray, blood tests, urine tests, etc.) During a follow-up period (day 1 to day 30): - referral to hospital - additional investigations (X-Ray, blood tests, urine tests, etc.) - patients with full clinical recovery at day 7 and day 30 - admission to hospital - mortality - cost-effectiveness - patient satisfaction - qualitative study: endpoints On day of index consultation and/or during follow up (from day 0 to day 30)): - the proportion of subjects who actually took antibiotics
Planned Sample Size	7000
Timing of the intervention	Intervention at **index** consultation (at presentation to primary care)
Follow-up duration	**30 days** follow-up
Duration of the trial (FPI-CSR)	45 months

FUNDING AND SUPPORT IN KIND

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

ROLE OF STUDY SPONSOR AND FUNDER

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

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES

Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. The TSC includes members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC will monitor trial progress, conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

The TSC is composed of the following participants:

- Academic Centre for General Practice (ACHG), KU Leuven: Jan Verbakel, Ann Van den Bruel, Tine De Burghgraeve, Nicolas Delvaux
- UZ Leuven Clinical Trial Centre: Ine Vanopdenbosch
- Department of Family Medicine and Primary Health Care, UGent: An De Sutter, Stefan Heytens
- Department of General Practice, U Antwerp: Sibyl Anthierens, Samuel Coenen
- Department of Family Medicine, VUB: Dirk Devroey
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- Leuven Biostatistics and Statistical Bioinformatics Centre, KU Leuven: Annouschka Laenen
- Leuven Institute for Healthcare Policy, KU Leuven: Jeroen Luyten
- Representative French and Dutch speaking GPs
- PPI-representatives
- Paediatrics UZLeuven: Lars Desmet, Paediatric Intensive Care Physician
- Laboratory Medicine: UZA, Viviane Van Hoof, Clinical Biologist
- Laboratory Medicine UZLeuven: Ann Verdonck, Pharmacist Clinical Biologist

KCE shall have the right (but not the obligation) to be present at each TSC meeting (more details can be found in the research agreement template).

The TSC will meet on average 3 times per year the first year and twice a year after that. The TSC is composed of the CI, the trial statistician, the trial PM, a representative of other participating centres or groups, up to 2 patients or members of the public, 1 representative of the sponsor, 1 representative of the funder.

The day-to-day management of the study will be performed by the Trial Management Group (TMG) which is distinct from the TSC and consists of the chief investigator and the trial coordinators.

TRIAL FLOW CHART

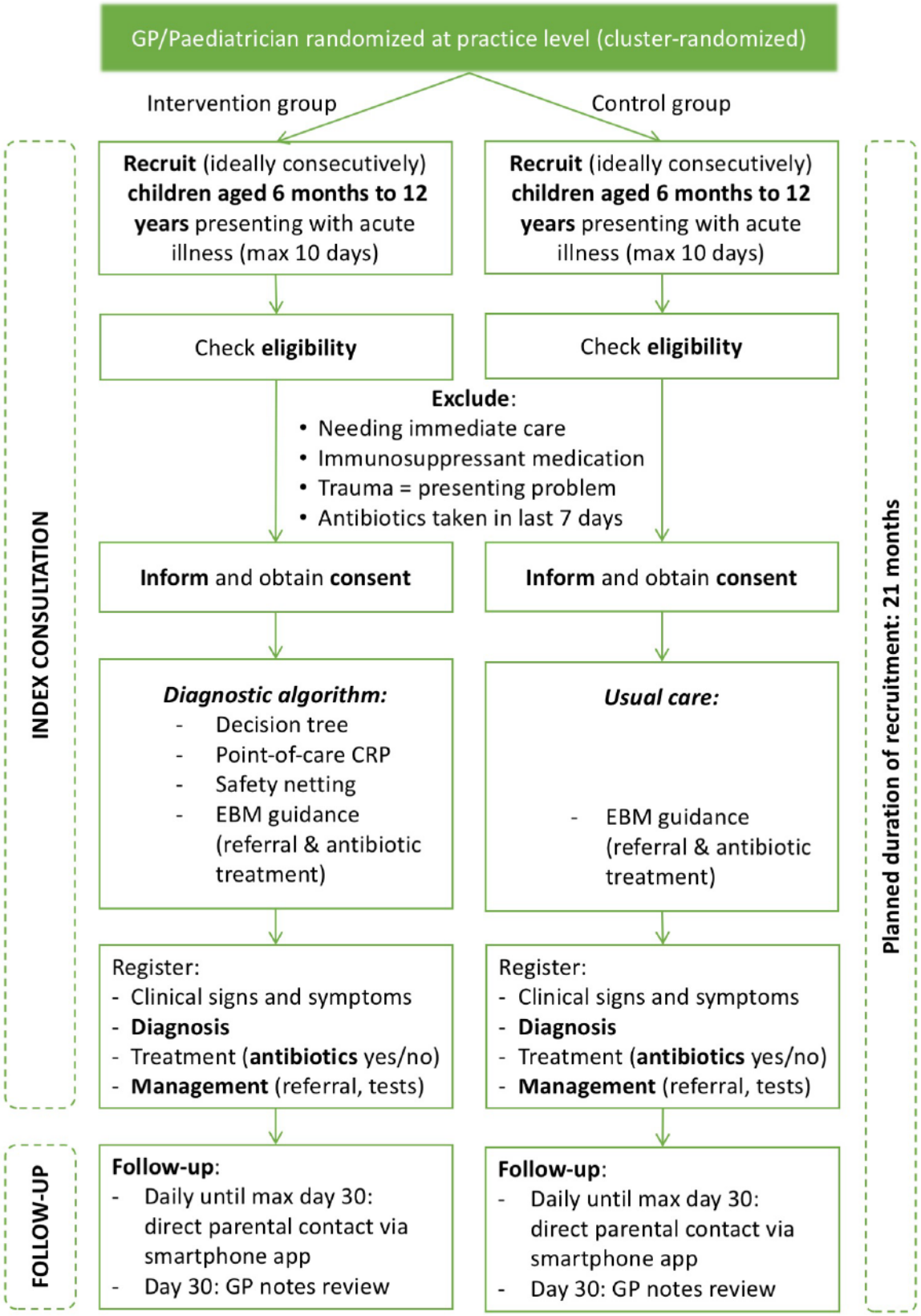

Figure 1 Flow chart ARON project

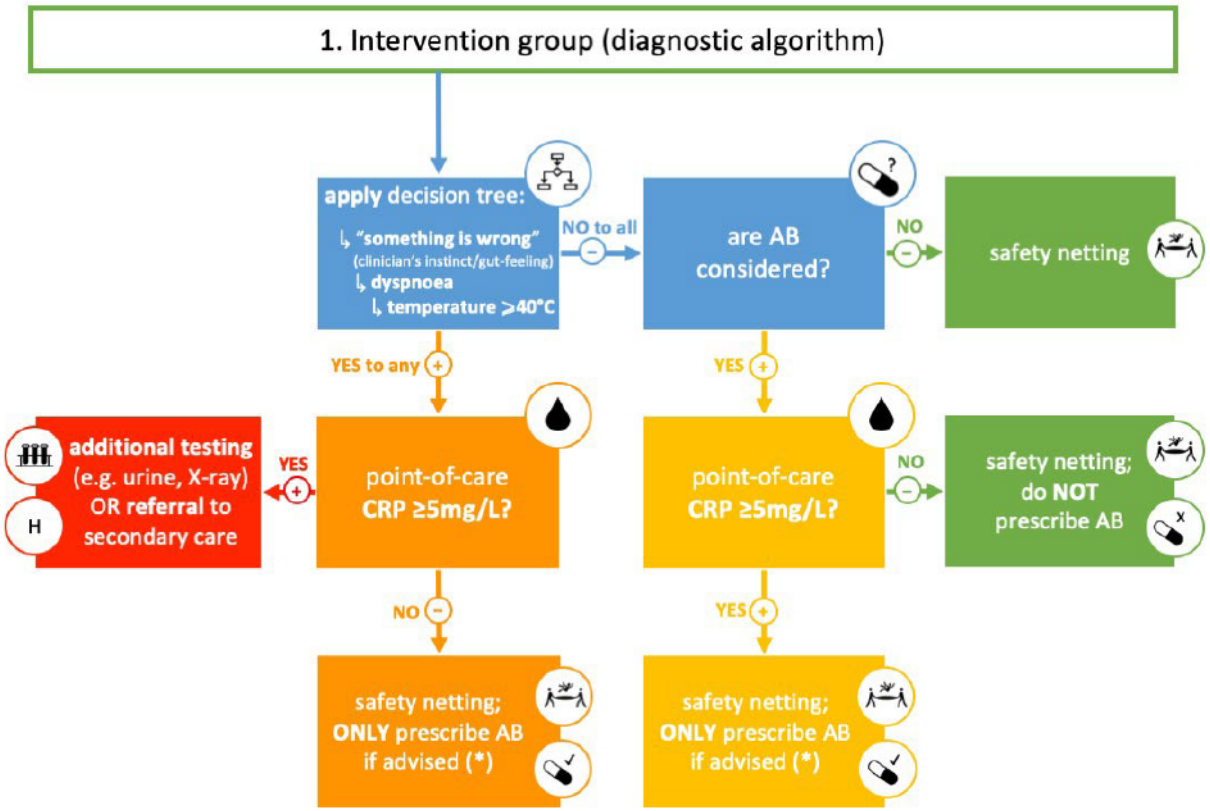

Figure 2 intervention arm: detailed flowchart

: decision tree, : point-of-care CRP test, : antibiotic treatment, : safety netting advice, : additional testing, **H**: referral to secondary care

Figure 2 describes the different steps of the diagnostic algorithm. First of all, the decision tree will be applied, if yes to any of three features (gut-feeling, dyspnea, temperature ≥40°C), physicians are advised to perform a point-of-care CRP test. If the CRP level is then 5 mg/L or above: referral or additional testing is advised to rule out a potential serious infection. If all features of the decision tree are reassuring (no to all) and a physician is still considering prescribing antibiotics, we advise them to perform a point-of-care CRP test and only consider prescribing if the CRP level is 5 mg/L or above. For example, in a child with dyspnoea and a CRP level of <5mg/L, physicians are advised to prescribe antibiotics only if according to the prescribing guidelines.

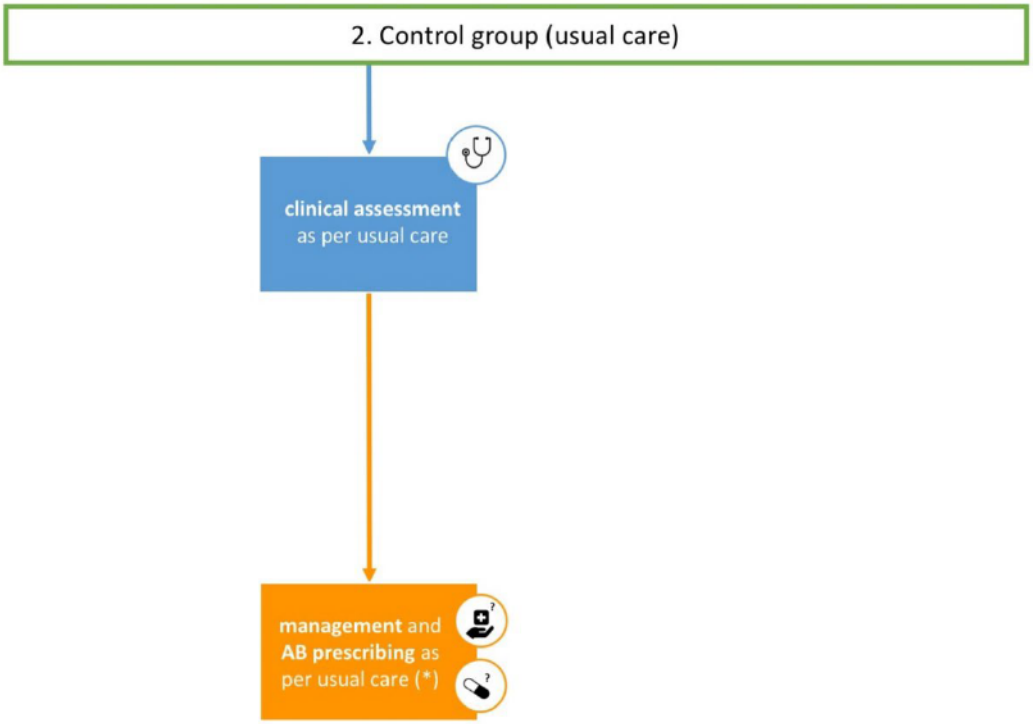

Figure 3 control arm: detailed flowchart

: clinical assessment, : clinical management, : antibiotic treatment

(*) Guidance on antibiotic prescribing (BAPCOC guide (November 2019) + RIZIV consensus meeting)		
Preliminary diagnosis	**Required criteria for rational antibiotics prescribing or referral**	**1st choice AB treatment**
Bronchiolitis	**Antibiotics**: not indicated **Referral:** clinical deterioration; <3 months; breathing rate >60/'; reduced intake	none
Bronchitis (acute)	**Antibiotics**: fever >38.5°C; cough, tachypnoea, reduced/muffled lung sounds, crepitations, lab or radiology tests suggestive of bacterial pneumonia **Referral**: <3 months; persistent vomiting or high fever; breathing rate >50/'; nasal flaring; moaning; chest wall retractions; oxygen saturation <92%; appearing seriously ill; reduced fluid intake; chronic condition; suspected pleural effusion; adequate home treatment not feasible; parental concern illness is different from previous illnesses	**amoxicilline** 100 mg/kg/d for 5 d
Epiglottitis (acute)	**Antibiotics:** IV treatment needed requiring hospital admission **Referral**: immediate referral to hospital	Immediate referral
Erysipelas	**Antibiotics**: always indicated **Referral**: <3 years of age	**flucloxacilline** 100 mg/kg/d for 10 d
Gastroenteritis with diarrhoea	**Antibiotics**: fever ≥ 38.5°C; bloody diarrhoea; appearing seriously ill **Referral**: sepsis, severe dehydration	**azithromycine** 10 mg/kg/d for 3 d
Impetigo	**Antibiotics**: systemic symptoms; adenopathy; failure local therapy **Referral:** failure of oral treatment (no improvement after 48 hours)	**flucloxacilline** 50-100 mg/kg/d for 7 d
Otitis media (acute)	**Antibiotics**: <6 months; Down syndrome; previous ear surgery or anatomic ORL abnormalities; immunodeficiency; appearing seriously ill; fever >39°C; persistent fever or pain ≥3 days; (bilateral AOM; persistent otorrhoea) **Referral:** <1 month; suspected complication (mastoiditis); persistent otorrhoea >6 weeks	**amoxicilline** 75-100 mg/kg/d for 5 d
Pertussis	**Antibiotics**: not indicated **Referral**: <1 year of age	none
Pneumonia	**Antibiotics**: always indicated **Referral**: same criteria as bronchitis	**amoxicilline** 100 mg/kg/d for 5 d
Sinusitis (acute)	**Antibiotics**: appearing seriously ill; high fever; no improvement after 10-15 days **Referral:** suspected complication; immunodeficiency	**amoxicilline** 75-100 mg/kg/d for 5 d
Tonsillitis (acute)	**Antibiotics**: Appearing seriously ill or less eating/drinking, high fever, immunodeficiency **Referral:** clinical deterioration; upper airway obstruction; peritonsillar abces	**fenoxymethylpenicilline** 50 000 IE/kg/d for 7 d
Urinary tract infection (cystitis or pyelonephritis)	**Antibiotics:** if 1st episode of cystitis in girls >5 years **Referral:** all children, unless 1st episode of cystitis in girl >5 years	cystitis: **nitrofurantoïne** 5-7 mg/kg/d for 5 d pyelonefritis: **cefuroxim axetil** 30-45 mg/kg/d for 5 d

Figure 4 guidance on antibiotic prescribing (BAPCOC guide (November 2019) + RIZIV consensus meeting)

■ STUDY PROTOCOL

1 BACKGROUND

Children become ill quite often, mainly caused by **infections** and most can be managed in the **community**. However, many children are prescribed **antibiotics (AB)** which contributes to **antimicrobial resistance** and reinforces health-seeking behaviour.

Ambulatory care is where most AB are prescribed, especially for respiratory infections. Children are at particularly high-risk for unnecessary AB prescribing (up to 37%)(1,2) and up to 1 in 4 children receives at least one AB prescription/year from their general practitioner.(3,4)

The care for acutely ill children has traditionally been a **primary care** responsibility,(5) but increasing numbers are seen in hospital. There has been a 40% increase in the number of children presenting to the emergency department (UK) over the last decade (14% with febrile illness),(6) with urgent hospital admission rates increasing by 28%, mostly for acute infections, with 23 per 1000 children admitted annually for a condition that could be managed in the community.(7,8)

In contrast, **serious infections** have become **rare** (<1% of childhood infections).(9) **Pneumonia** represents four-fifth of all cases,(10,11) followed by **urinary tract infections**, and very few cases of **sepsis** or **meningitis**,(12) in which prompt recognition is essential to avoid complications or death.(13) However, the clinical presentation in ambulatory care is highly non-specific, especially in the early stages of illness.

Clinicians often cite **diagnostic uncertainty** as a reason to prescribe antibiotics. **Diagnostic uncertainty** leads to inappropriate care escalation for patients with non-serious infections, and is a major driver for unplanned **hospital**

admissions,(14) which add further pressure to already stretched healthcare services; in Belgium, medical hospital admissions are increasing by 1% per year.(15)

Only one clinical **decision tree** has been developed (n=3981) and externally validated (n=3142) for primary care, with **100% sensitivity** and **81% specificity**,(9,12) for **diagnosing serious infections** in children, testing positive if yes to any of three features: **clinician gut feeling, dyspnea and body temperature ≥40°C**. The rule achieves a safe and complete rule-out of serious infections but still leaves 1 in 5 children in whom uncertainty remains.

Introducing better diagnostic tests might strengthen the ambulatory care management of acutely ill children. Inflammatory markers such as C-reactive protein (**CRP**) and procalcitonin can assist in diagnosing serious infections in hospital settings.(16) Up until now, such blood tests play only a relative marginal role in ambulatory care because the result comes back from the laboratory too late to influence clinical decision-making.(10) In an international survey, primary care doctors identified infections as a key area for diagnostic innovation, in particular for point-of-care tests.(17)

Evidence on innovative diagnostics from ambulatory care is scant and haphazard; translating evidence from hospitals to ambulatory care is problematic because accuracy and impact of diagnostic tests are setting-dependent,(9) and good quality studies in ambulatory care are **urgently needed** to direct implementation.

Point-of-care (POC) platforms that test CRP within **4 minutes** have now become available,(18,19) and have been introduced in Belgian primary care through several competitive companies developing high-standard POC devices.

We previously established that **POC CRP** testing should be restricted to children at higher risk after clinical assessment with the decision tree and a CRP threshold <5 mg/L **rules out serious infection** with 100% certainty in another 10% of the population, potentially avoiding **unnecessary hospital referrals** and/or **additional testing.(11)** This further empowers clinicians to **safely** manage children in ambulatory care, identifying children with a serious infection without swamping secondary care services.(20,21)

POC CRP testing may also **reduce AB prescribing** to acutely ill children in primary care. A recent review of the literature showed that using **CRP** as a **POC test** reduces antibiotic prescriptions in children if **guidance** is provided. We summarized all available published evidence up to 2017 in a systematic literature review, and found that **AB prescriptions by primary care physicians decrease** (up to 44%) only if **clear instructions** on how to interpret the result of the CRP test are provided.(22,23) However, these instructions were based either on evidence from studies performed on adult patients or on expert opinion, which could result in inappropriate prescribing in children.

We interviewed parents and clinicians who took part in a study on POC CRP and found general **support** for the test, but the doctors wanted **specific guidance** on how to deal with the test result.

Our previous studies now provide solid evidence for **children-specific thresholds**, safe for **ruling out serious infections** and fit for **guiding AB prescribing**.

2 RATIONALE

We aim to strengthen the assessment of acutely ill children in **primary care**, by introducing a **diagnostic algorithm** that can **decrease antibiotic prescribing**.

In light of the prior evidence and its results so far, the **ARON trial** will test the **impact of a diagnostic algorithm** including **a standardised clinical assessment**, a **POC CRP test**, and **safety netting advice**.

Therefore, we propose to assess the clinical and cost-effectiveness of a **diagnostic algorithm** which includes a **decision tree, POC CRP** and **safety netting advice** in acutely ill children aged **6 months to 12 years** of age presenting to ambulatory care, on **AB prescribing, referral/admission to hospital, additional testing, mortality**, and **patient satisfaction**.

More specifically, our **research question** is **whether this diagnostic algorithm is able to safely reduce antibiotic prescribing in acutely ill children presenting to ambulatory care.**

The decision whether or not to conduct a POC CRP test will depend on the standardized clinical assessment, i.e. our validated clinical decision tree, and subsequently for low-risk children on the intention to prescribe AB. (see Flowchart)

We will provide clear evidence-based guidance on how to interpret the CRP test result as outlined below. (see Flowchart)

A **process evaluation** will examine how clinicians use CRP testing in their practice and how parents experience these consultations.

We propose a study, where practices recruiting children (**6 months to 12 years** of age) will be randomized to either (a) a **diagnostic algorithm** with **CRP** testing and specific guidance on when to prescribe AB or (b) usual care. CRP testing will be done using a **finger prick** test (result within 4 minutes). The CRP level will then be given to the clinician who will communicate the result to the child/parents.

We aim to recruit 7000 children and will collect data registered by the participating physician, from the child's health record and children/parents directly. We will describe how the intervention has worked in practice and how clinicians/parents have experienced these consultations.

Guidance will be part of a **diagnostic algorithm** which includes **clinically guided POC CRP** testing and **safety netting advice** to inform parents on what to expect and what to look out for.

Individual **interviews** will be conducted with clinicians and parents taking part in the trial within 30 days after the first contact consultation, to explore the social processes influencing embedding of the intervention within practice, and behaviour change techniques.

These individual telephone interviews will be performed with a selection of parents to address whether their concerns were discussed appropriately and whether their expectations were met and how they experienced the consultation and/or POC CRP testing.

The safety-netting advice will be supported by a parent **information booklet**, based on previous research (the "When should I worry"-interactive booklet (a guide to Coughs, Colds, Earache & Sore Throats), the "Mijn kind heeft koorts" booklet (Eefje de Bont, www.thuisarts.nl), and the "Caring for children with coughs"-leaflet (information about how to look after a child who has a cough and when to see the doctor)).

The findings of this study could **change** the practice of ambulatory care physicians and might be of great interest to parents and childcare providers. We will publish the findings of this research in academic journals, present at national conferences and discuss results with groups responsible for the national guidance on how to assess acutely ill children (Domus Medica, SSMG).

3 ASSESSMENT AND MANAGEMENT OF RISK

This clinical trial is a low risk intervention clinical trial, because:

- the use of the clinical algorithm is not associated with any risk for the patient, other than offering the clinician advice regarding prescribing or referral decisions, which the clinician can choose to overrule if a clear indication is present to do so.
- the POC CRP test used in our trial should have proven to be analytically accurate as well as already be marketed for commercial medical use in Belgium, so the risk associated with the device is expected to be low. The focus of our trial is not examining the accuracy of the device itself.
- the additional diagnostic questions and follow-up are not associated with an additional risk to the safety of the study participants and pose only a minimal burden as compared to normal clinical practice and most of these questions are already part of usual care.

4 OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES

4.1 Primary objective

The **ARON trial** will test the **impact of a diagnostic algorithm** including **a standardised clinical assessment,** a **POC CRP test,** and **safety netting advice**.

More specifically, our **research question** is **whether this diagnostic algorithm is able to safely reduce antibiotic prescribing in acutely ill children presenting to ambulatory care.**

The main aim of our study is to establish the assumed superiority of a **diagnostic algorithm** including a standardised clinical assessment, a POC CRP test and safety netting advice over usual care to reduce **antibiotic prescribing rates** (both immediate and delayed prescribing).

Null hypothesis: the diagnostic algorithm including a standardised clinical assessment, a POC CRP test and safety netting advice will not reduce the proportion of subjects receiving a prescription for immediate or delayed antibiotic treatment at the index consultation compared to usual care

Alternative hypothesis: the diagnostic algorithm including a standardised clinical assessment and a POC CRP test with EBM guided advice will reduce the proportion of subjects receiving a prescription for immediate or delayed antibiotic treatment at the index consultation compared to usual care

The **primary outcome** is antibiotic prescribing rate at index consultation (immediate or delayed) (day 0).

Any reduction in the use of antibiotics should be considered alongside any negative effect on the well-being of a child. Therefore, time until full clinical recovery, additional investigations, re-consultations and antibiotics prescribed during follow-up (secondary outcomes) should be considered alongside any potential reduction in antibiotic use (primary outcome).

P Children aged **6 months to 12 years** of age with an **acute illness** episode presenting to in-hours general practices or community paediatrics offices

I **Diagnostic algorithm** including a standardised clinical assessment, a POC CRP test and safety netting advice

C Diagnosis and treatment/management as per **usual care**

O **Antibiotic prescribing rate** at index consultation (immediate or delayed)

T This outcome will be registered **immediately** at the index consultation

4.2 Secondary objectives

4.2.1. Clinical recovery during follow-up

The first **secondary outcome** is time until full clinical recovery (in days) during follow-up (day 1 to day 30).

Null hypothesis: the diagnostic algorithm including a standardised clinical assessment, a POC CRP test and safety netting advice is inferior to usual care in terms of the number of days until subjects reach full clinical recovery

Alternative hypothesis: the diagnostic algorithm including a standardised clinical assessment, a POC CRP test and safety netting advice is not inferior to usual care in terms of the number of days until subjects reach full clinical recovery

P Children aged **6 months to 12 years** of age with an **acute illness** episode presenting to in-hours general practices or community paediatrics offices

I **Diagnostic algorithm** including a standardised clinical assessment, a POC CRP test and safety netting advice

C Diagnosis and treatment/management as per **usual care**

O number of days until full **clinical recovery**

T clinical This outcome will be checked from the diary (via app for parents) from day 1 until day of full recovery

4.2.2. Additional investigations at index consultation and/or during follow-up

The second **secondary outcome** is additional investigations (X-Ray, blood tests, urine tests, etc.) at the index consultation (day 0) and/or during follow-up (day 1 to day 30).

Null hypothesis: the diagnostic algorithm including a standardised clinical assessment, a POC CRP test and safety netting advice is inferior to usual care in terms of the proportion of subjects receiving additional investigations (X-Ray, blood tests, urine tests, etc.) at the index consultation and/or during follow-up.

Alternative hypothesis: the diagnostic algorithm including a standardised clinical assessment, a POC CRP test and safety netting advice is not inferior to usual care in terms of the proportion of subjects receiving additional investigations (X-Ray, blood tests, urine tests, etc.) at the index consultation and/or during follow-up.

P Children aged **6 months to 12 years** of age with an **acute illness** episode presenting to in-hours general practices or community paediatrics offices

I **Diagnostic algorithm** including a standardised clinical assessment, a POC CRP test and safety netting advice

C Diagnosis and treatment/management as per **usual care**

O **Additional investigations** (X-Ray, blood tests, urine tests, etc.) at the index consultation and/or during follow-up

T This composite outcome will be registered **immediately** at the index consultation and/or checked from the patient health record from day 1 to day 30 after the index consultation

4.2.3. Re-consultation during follow-up

The third **secondary outcome** is re-consultation with their physician during follow-up (day 1 to day 30).

Null hypothesis: the diagnostic algorithm including a standardised clinical assessment, a POC CRP test and safety netting advice is inferior to usual care in terms of the proportion of subjects re-consulted their physician during follow-up from day 1 to day 30

Alternative hypothesis: the diagnostic algorithm including a standardised clinical assessment, a POC CRP test and safety netting advice is not inferior to usual care in terms of the proportion of subjects re-consulted their physician during follow-up from day 1 to day 30

P Children aged **6 months to 12 years** of age with an **acute illness** episode presenting to in-hours general practices or community paediatrics offices

I **Diagnostic algorithm** including a standardised clinical assessment, a POC CRP test and safety netting advice

C Diagnosis and treatment/management as per **usual care**

O **Re-consultation** during follow-up from day 1 to day 30

T This outcome will be checked from the patient health record from day 1 to day 30 after the index consultation

4.2.4. Antibiotic prescribing rate during follow-up

The fourth **secondary outcome** is antibiotic prescribing rate during follow-up (day 1 to day 30).

Null hypothesis: the diagnostic algorithm including a standardised clinical assessment, a POC CRP test and safety netting advice is inferior to usual care in terms of the proportion of subjects receiving a prescription for immediate or delayed antibiotic treatment during follow-up from day 1 to day 30 compared to usual care

Alternative hypothesis: the diagnostic algorithm including a standardised clinical assessment, a POC CRP test and safety netting advice is not inferior to usual care in terms of the proportion of subjects receiving a prescription for immediate or delayed antibiotic treatment during follow-up from day 1 to day 30 compared to usual care

P Children aged **6 months to 12 years** of age with an **acute illness** episode presenting to in-hours general practices or community paediatrics offices

I **Diagnostic algorithm** including a standardised clinical assessment, a POC CRP test and safety netting advice

C Diagnosis and treatment/management as per **usual care**

O **Antibiotic prescribing rate** during follow-up from day 1 to day 30

T This outcome will be checked from the patient health record from day 1 to day 30 after the index consultation

4.3 Primary endpoint

The primary outcome is the proportion of subjects who were prescribed antibiotic treatment (both immediate and delayed) at the index consultation as recorded by the treating physician.

4.4 Secondary endpoints

- the duration (in days) until reaching full clinical recovery
- the proportion of subjects receiving additional testing (including, but not limited to (X-Ray, blood tests, urine tests) at index consultation (day 0) and/or during follow-up (day 1 to day 30)
- the proportion of subjects who re-consulted their physician during follow-up (day 0 to day 30)
- the proportion of subjects who were prescribed antibiotic treatment during follow-up (immediately after index consultation to day 30)

4.5 Exploratory endpoints

- the proportion of subjects receiving additional testing (including, but not limited to (X-Ray, blood tests, urine tests) at index consultation (day 0)
- the proportion of subjects receiving additional testing (including, but not limited to (X-Ray, blood tests, urine tests) during follow-up (day 1 to day 30)
- the proportion of subjects referred to hospital at index consultation (day 0)
- the proportion of subjects referred to hospital during follow-up (day 1 to day 30)
- the proportion of subjects admitted to hospital at index consultation (day 0)
- the proportion of subjects admitted to hospital during follow-up (day 1 to day 30)
- the proportion of subjects who died at index consultation (day 0)

- the proportion of subjects who died during follow-up (day 1 to day 30)
- the proportion of subjects with full clinical recovery at day 7
- the proportion of subjects with full clinical recovery at day 30
- Patient's satisfaction (as part of the nested qualitative study)
- Parent's satisfaction (as part of the nested qualitative study)
- Physician's satisfaction (as part of the nested qualitative study)
- Cost-effectiveness of the intervention: healthcare expenditures in terms of hospitalization, consultations, pharmaceuticals (reimbursed and non-reimbursed), productivity, quality of life
- Adherence to the diagnostic algorithm
- the proportion of subjects who actually took antibiotics (from day 0 to Day 30)

5 TRIAL DESIGN

This study is a pragmatic cluster randomised controlled superiority trial:

multicentre:	6 academic centres for primary care will be involved in the recruitment of 122 primary care practices
pragmatic:	criteria excluding patients from participation will be limited as well as procedures that do not reflect care as usual
cluster:	randomisation occurs at the level of the primary care practice while patients are the unit of analysis
randomised:	block randomization per academic centre will be performed to assign primary care practices to either the intervention or the control arm
controlled:	the intervention will be compared with usual care
superiority:	the trial is designed to show that the intervention is superior to usual care

The rationale for choosing a cluster design is to prevent contamination across the intervention and control arm. The cluster and unit of randomization is the physician's practice. There will be 2 arms - the intervention arm and the usual care arm - in 50:50 ratio.

6 STUDY SETTING

As the majority of acutely ill children are seen out of hospital by general practitioners and community paediatricians, the study will be conducted in 122 primary care or community paediatric practices throughout Belgium. The participating practices will be recruited by the academic centres for Primary Care of the KU Leuven, UGent, UAntwerpen, Université Liège, UCL and VUB (Brussels).

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria for practices

Practices' eligibility (and physicians within these practices) for inclusion in the study will be based on the following criteria:

- Being able to recruit acutely ill children (ideally consecutively)
- Agree to the terms of the clinical study agreement.

7.2 Exclusion criteria for physicians

Practices will be excluded from study participation based on the following criteria:

- Currently using a POC CRP device as part of their routine care

No practices will be excluded on other grounds than the above. Age, demographics, geographic region will not be used to exclude eligible practices. This will provide us with a real-life, representative subset of ambulatory care physicians.

7.3 Inclusion criteria for children

Patients' eligibility for inclusion in the study will be based on the following criteria:

- Children aged **6 months to 12 years,** provided informed consent can be obtained
- presenting with an **acute illness episode** that started maximum 10 days before the index consultation

7.4 Exclusion criteria for children

Patients will be excluded from study participation based on the following criteria:

- Children who were previously included in this trial
- children with an underlying known chronic condition (e.g. asthma, immune deficiency)
- clinically unstable warranting immediate care
- immunosuppressant medication taken in the previous 30 days
- trauma as the main presenting problem
- antibiotics taken in the previous 7 days
- Unwillingness or inability to provide informed consent

8 TRIAL PROCEDURES

8.1 Trial randomisation

In order to avoid contamination between physicians working in the same practice randomization will happen at the level of the general practice.

General practices and community paediatric centres will be randomized in one of the 2 study arms in a 1:1 ratio using a block randomization system stratified per recruiting academic centre in order to guarantee that allocation to either usual care or the intervention arm is balanced within every region.

Stratified block randomization will be done using an electronic random numbers generator in blocks of 4 practices. Randomisation and concealment will be centralised at the KU Leuven and conducted by a staff member not involved in data collection or delivering the intervention.

8.2 Blinding

Owing to study procedures, children, their parents and physicians will not be masked to the practices' random allocation.

8.3 Unblinding

Conditions and procedures for unblinding are not required as the participating physicians will be aware of their allocation.

8.4 Recruitment

Given the current special circumstances under the COVID-19 pandemic, we aim to recruit practices during two stages, with stage 1 acting as a run-in period before all practices will be asked to start recruiting patients. The first stage will allow the study team to recruit a smaller number of practices in a selection of the participating academic centres to further streamline the recruitment process and remedy any unforeseeable issues that might occur after the investigator meeting and study initiation. In a second stage more practices will be recruited both at the initial academic centres as well as the other participating academic centres. We aim to keep recruitment of practices as pragmatic as possible to limit the burden on practices dealing with the aftermath of the COVID-19 pandemic.

For the recruitment of general practices, each academic centre will regionally, according to their own customs for recruitment (and what training may be part of the recruitment process), approach physicians. A website with information about the trial could help the recruitment process. The website will contain a form, which can be completed by GPs. GP's can express their interest in the study without further obligations. The study teams of the

AC can contact the GP for a thorough explanation of the study, once approval of the ethics research committees is obtained. However, the information provided at the investigator meetings will be standardised and contain short and practical training on the new guidelines.

Both solo general practices and group practices are eligible for participation in the trial. Per general practice ideally only 1 or 2 physicians will be selected for participation in the study, in order not to dilute the number of patients per physician and thus to minimize the possibility of a strong selection of patients towards the most motivated - as perceived by the physician - and for practical reasons.

8.4.1 Patient identification

The participating physicians will be asked to (ideally) consecutively recruit children with an acute illness over the recruitment period covering two winter seasons.

Parents and children will be informed about the study by the physician. For that purpose, a patient information leaflet will be developed describing the aim and course of the trial and emphasizing the fact that it does allow the physician to overrule the clinical algorithm but aims to investigate whether the intervention may help reduce the antibiotic prescribing rate.

Parents and children willing to participate in the study will be asked to sign an informed consent form. Consent will be signed by the parents or legal guardian. We will include an age-adjusted assent procedure for older children (≥6 years).

8.4.2 Screening

The physician will assess eligibility and willingness to participate in the study. No additional procedures are required. The reasons for patient non-eligibility and non-participation - if provided - will be recorded in a designated screening log.

8.5 Consent

Eligible children (and their parents) will be informed by their physician about the study. Apart from a clear oral explanation, the parents will receive a comprehensive information leaflet.

All the information essential to the decision-making process of the participant will be provided including:

a. a brief, clear presentation of the rights of the participant (voluntary participation and confidentiality)
b. a clear description of the research project (context, objectives, inclusion/exclusion criteria, methodology & course) highlighting the constraints (point-if-care CRP testing) in addition to the standard treatment
c. descriptions of the risks & benefits
d. the right to withdraw from the study at any given point
e. the approval of the ethical committee
f. the researchers' contacts

Children and their parents will have the opportunity to ask questions about the study and sufficient time to make their decision. Children (and their parents) will be informed that they will still receive all the usual care, whether they choose to participate or not.

After that children and their parents will be asked officially to participate in the study. Consent will be signed by the parents or legal guardian. We will include an age-adjusted assent procedure for older children (≥6 years).

Some practices will be selected based on purposive sampling to take part in the nested qualitative study and will be provided with an additional sheet for the informed consent form to request permission from parents to be contacted by telephone (by a trained qualitative researcher of the study team) during follow-up to take part in a semi-structured interview.

8.6 Baseline data

At study entry, the following baseline data will be collected for each participating child:

- age

- gender

Data will be collected by the physician at the index consultation and entered in the eCRF.

8.7 Trial assessments

Assessment by physician

During the first consultation at baseline, a selection of **clinical features** will be assessed and recorded by the physician in the patient's health record and on the e-CRF, **including the clinical decision tree** (clinician's gut feeling, body temperature, dypnoea). **CRP testing** will be conducted as per the **diagnostic algorithm** as described above **(See Flowchart)**.

The physician will be asked to note in the patient's health record and on the e-CRF whether antibiotics were prescribed, whether this was an immediate or delayed prescription. If the decision to prescribe antibiotics diverted from the suggested algorithm in the intervention arm, physicians will be asked to acknowledge this and explain why on the e-CRF.

Any additional care during follow-up will be left at the discretion of the child's physician. We will use a **point- of-care CRP test** which requires 1.5 µl of capillary blood obtained by finger prick (results within 4 minutes). Clinical features will be recorded before the CRP test is conducted.

Follow-up (app)

Follow-up information for all children will be collected using direct patient/parent contact using a smartphone app. Information regarding the smartphone app as well as instructions on how to install will be handed to children and their parents at the baseline consultation.

The smartphone app will ask parents and/or children about daily symptoms such as body temperature, cough, treatment and whether they consulted a physician or went to the hospital. The daily follow-up will consist of a maximum of 10 short questions which are answered by ticking the appropriate box. Parents will be asked to complete these questions once a day until the symptoms have resolved and the child is considered cured of the acute illness.

Furthermore, the app will ask parents to complete a few quality-of-life items (proxy version of the EQ-5D-Y questionnaire)(24) and two pain scales (Wong Baker FACES Pain Scale, FLACC scale)(25,26) during follow-up. Some items will be requested daily (visual analogue scale of the proxy version of the EQ-5-D and the Wong Baker FACES Pain Scale), whereas other items will be presented weekly and/or until the child is feeling better (all items of the proxy version of the EQ-5D-Y and the FLACC scale). We will ask parents to complete these questions.

Follow-up (patient health record)

Follow-up information for all children will be collected from the patient health record up to 30 days after the index consultation. This information will be collected by the participating GP (follow-up form in the eCRF will be due 30 days after the index consultation) with or without support of a flying nurse during on-site visits after blocks of patients included. Follow-up information will consist of: diagnosis of a serious infection, re-attendance visits, medication prescribed, use of additional tests, admission to hospital, death, prioritizing the data related to safety events (mortality, admission to hospital, detection of a serious infection) as these would need to be assessed first in the eCRF, allowing appropriate safety measures to be put in place.

Interviews as part of the nested qualitative study

Individual telephone interviews will be conducted with a small selection of clinicians (approximately 16) and a selection of parents (approximately 14 to 18) taking part in the trial (nested qualitative study), to explore the social processes influencing embedding of the intervention within practice, and behaviour change techniques.

8.8 Flow chart of trial procedures

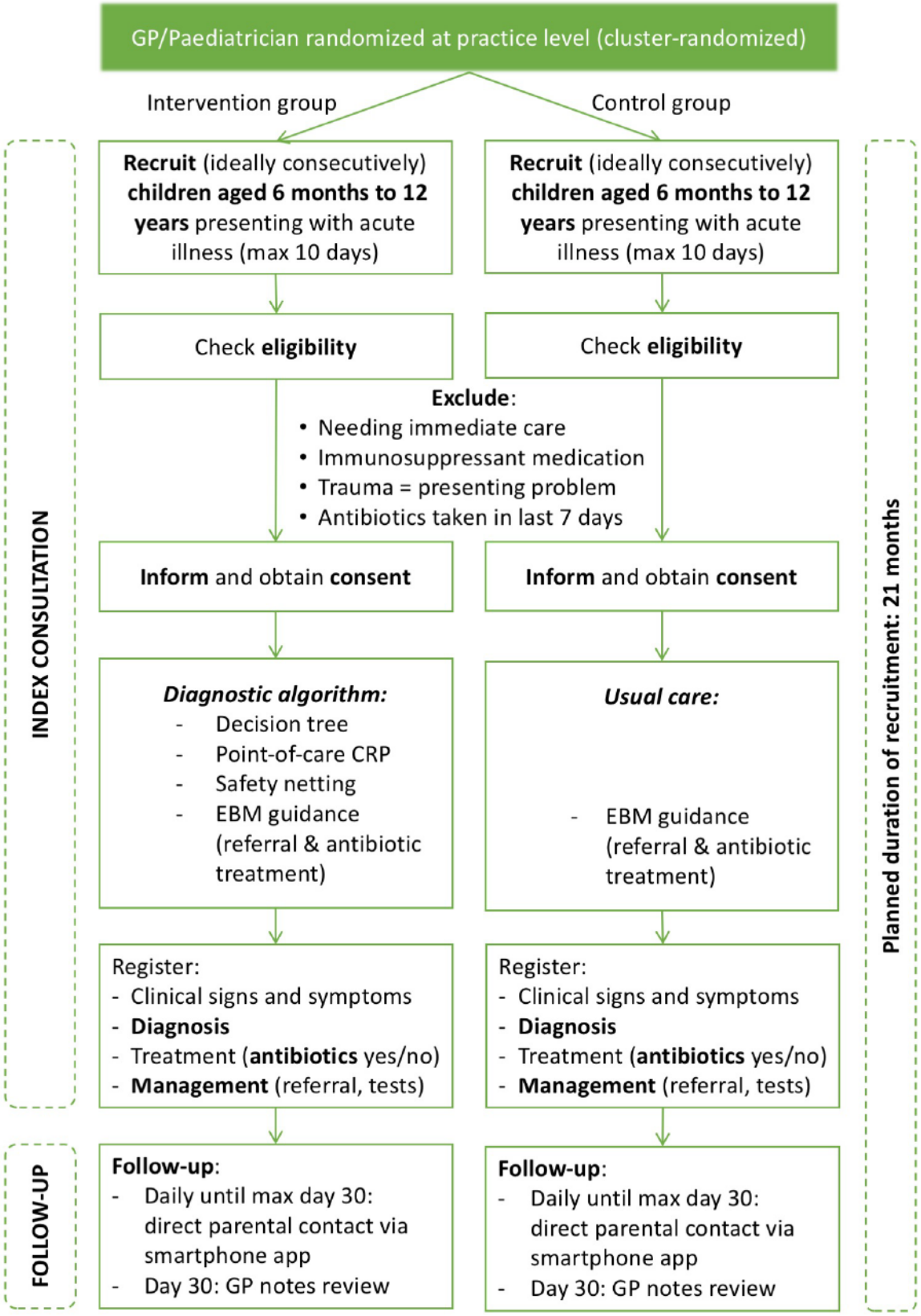

Figure 5 Flow chart ARON project

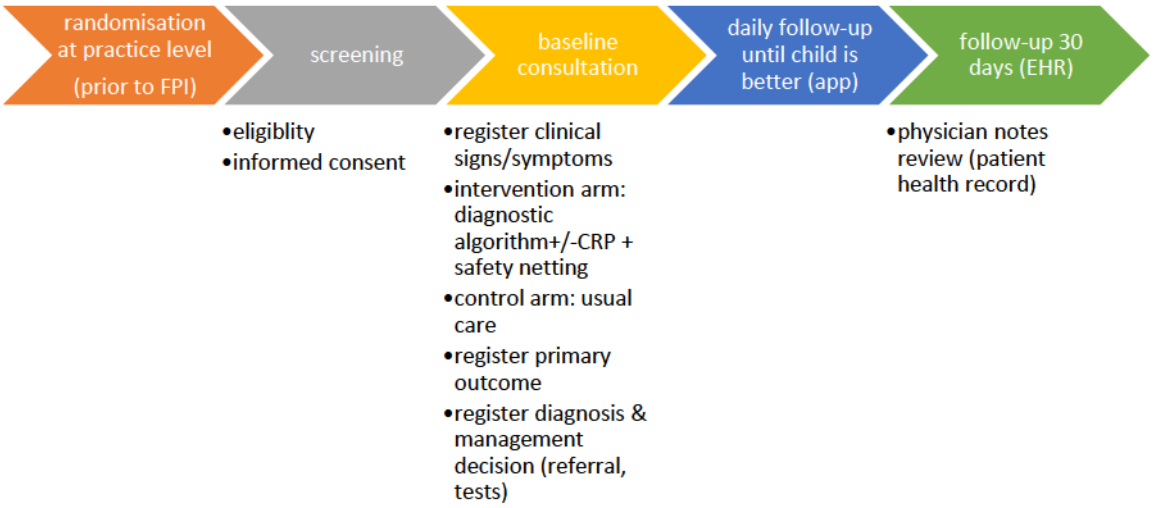

Figure 6 flow chart trial procedures

8.9 Qualitative assessments – Nested studies

A process evaluation will be nested within the pragmatic clustered randomized trial. The process evaluation will capture data to understand how the intervention is used and viewed by physicians and patients. This is important for informing implementation in practice. It will explain how physicians and patients experience the intervention. We aim to identify factors within each arm which influence the behaviour to prescribe antibiotic treatment whilst taking part in the intervention arm or whilst receiving usual care in order to build a framework describing the mechanisms required for successful implementation.

Individual telephone interviews will be conducted with physicians and parents taking part in the trial. Interviews will be carried out to capture perceived barriers and facilitators to using the diagnostic algorithm including POC CRP testing approach or with the usual care approach. Physicians (approximately 16, minimum 8 French-speaking and 8 Flemish-speaking) will be purposively sampled to obtain variation in gender, practice setting and experience. Parents (approximately 14-18) will be purposively sampled to obtain variation in age, age and the number of children, socio-demographic background, gender and whether they received antibiotics. Interviews will follow semi-structured topic guides exploring physicians' and parents' views and experiences of taking part in the trial. These individual telephone interviews will be performed with a selection of parents to address whether their concerns were discussed appropriately and whether their expectations were met and how they experienced the consultation and/or POC CRP testing.

Topic guides will be informed by existing literature and theory of health behaviour to ensure that questions elicit likely key determinants of behaviour. Topic guides will be piloted with patient representatives and clinicians. Interviews will be carried out by telephone and analysed using thematic and Framework analysis. These telephone interviews will indeed be performed by someone with the required skills and expertise in qualitative methods. This nested study will also be submitted for ethical review as an amendment to the main trial protocol.

8.10 Withdrawal criteria

Withdrawal from the study can be initiated either by the child, their parents or by the physician.

As stated in the Informed Consent, children and their parents have the right to end her/his participation in the trial at any point in time and for any reason. In case a child or parent wishes to end her/his participation, she/he can do so either by notifying her/his physician.

The treating physician can also consider a child for withdrawal from the study. However, the physician will have to discuss this option with the study coordinator and to receive the consent of the latter before the final decision of withdrawal can be made.

In all instances, the reason for withdrawal will be asked for and notified.

Withdrawn children will not be replaced.

8.10.1 Discontinuation of trial follow-up

If the follow-up is stopped early, the reason should be recorded in the patient's health records and be reported on the appropriate CRF whether it is due to either the patient's, parent/legal guardian's or clinician's decision. Reasons for stopping protocol treatment may include, but are not limited to:

- The patient and/or patient's parent/guardian does not wish to continue with further trial follow-up.

The trial will be analysed on an intention-to-treat (ITT) basis and all patients who stop follow-up will remain in the trial unless the patient and/or parent/legal guardian explicitly withdraws consent for data collection.

8.10.2 Discontinuation of trial procedures (if applicable)

Patients who discontinue trials procedures will be included in the final analyses of the primary outcome as these are registered at the baseline consultation, given informed consent was obtained.

8.10.3 Withdrawal of consent (discontinuation of trial participation)

The patient and/or parent/legal guardian may withdraw consent at any time during the study. For the purposes of this trial, withdrawal is defined as:

- The patient and/or parent/legal guardian would like to withdraw consent from study and is not willing to be followed up for the purposes of the trial at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the trial analysis).

The details of withdrawal should be clearly documented in the patient's health records and in the eCRF.

8.10.4 Loss to follow-up

If a patient is lost to follow-up, every effort should be made to contact the patient's physician to obtain information on the patient's status. Similarly, if a patient's care is transferred to another clinician, every effort should be made so that follow-up information will be obtained.

8.11 End of trial

End of a trial means the last visit of the last child, including collection of the follow-up data up to 30 days after the index consultation.

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

9 TRIAL INTERVENTION

Care as usual

In the control arm, patients will receive 'usual care' left at the discretion of the treating physician.

Apart from the general training session for all participating physicians they have attended prior to recruitment and randomization, physicians in the control arm will not receive additional tools.

They are expected (but not forced) to follow the Belgian guidelines (as described in "BAPCOC National guidelines and the RIZIV consensus meeting "Rational use of antibiotics in children"). (Figure 2)

9.1 Name and description of intervention(s)

Intervention: diagnostic algorithm

Guidance will be part of a **diagnostic algorithm** which includes **clinically guided POC CRP** testing and **safety netting advice** to inform parents on what to expect and what to look out for.

The safety-netting advice will be supported by a parent information booklet, based on previous research (the "When should I worry"-interactive booklet (a guide to Coughs, Colds, Earache & Sore Throats), the "Mijn kind heeft koorts" booklet (Eefje de Bont, www.thuisarts.nl), and the "Caring for children with coughs"-leaflet (information about how to look after a child who has a cough and when to see the doctor)).

They are expected (but not forced) to follow the Belgian guidelines (as described in "BAPCOC National guidelines and the RIZIV consensus meeting "Rational use of antibiotics in children"). (Figure 2)

9.2 Legal status of the intervention

The trial is being carried out under a Clinical Trial Authorisation (CTA). The POC CRP device is therefore only to be used by the named investigators, for the patients specified in this protocol, and within the trial.

9.3 Assessment of compliance

The follow-up will not contain any patient identifiable information (of the child or parent). A built-in system will be developed for the follow-up app allowing to track users as they register daily follow-up. Furthermore, each time the user performs specific actions (such as filling in the diary, answering questions etc.) this will be recorded.

10 SAFETY RECORDING AND REPORTING

The risk of adverse events occurring as a consequence of the intervention in this trial is unlikely therefore safety reporting will be limited to the safety reporting that is necessary in routine care (https://www.fagg-afmps.be/nl/notification_effets/humane_geneesmiddelenbewaking/melding_gezondheidszorgbeoefenaars).

Any safety events related to the device, which is CE marked and used within the intended use, will follow the usual reporting/materiovigilance requirements.

All safety parameters (e.g. mortality, admission to hospital) are collected in the eCRF and are prioritized over other follow-up data and monitored by the academic research team (monthly remote follow-up contact) and data managers. Any potential safety events detected by means of the follow-up data as part of the eCRF will be assessed during the regular trial steering committee meetings after the first winter season and then annually.

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11 STATISTICS AND DATA ANALYSIS

11.1 Sample size calculation

11.1.1 Initial sample size calculation before the start of the trial

Primary outcome

The main aim of our study is to establish the assumed superiority of a **diagnostic algorithm** including a standardized clinical assessment, a POC CRP test, and safety netting advice over usual care to reduce **antibiotic prescribing rates**.

Previous research in a similar population has shown approximately **17%** of children testing positive if yes to any of three features: clinician gut feeling, dyspnea and body temperature ≥40°C. (12) In all children, **30.43%** will be prescribed antibiotics.(22)

The outcome(s) on which the sample size calculation is based is the antibiotic prescribing rate at the first contact baseline consultation.

In children testing positive on the clinical decision tree, we found in the ERNIE2 trial (22), that:

- CRP was <5 mg/L in 28% of children testing positive on the clinical decision tree
- CRP was ≥5mg/L in 72% of children testing positive on the clinical decision tree
- of children testing positive on the clinical decision tree with CRP <5 mg/L: 29% received antibiotics, in 24% evidence-based guidelines advised to prescribe antibiotics and in 67% evidence-based guidelines advised to withhold antibiotics
- of children testing positive on the clinical decision tree with CRP ≥5 mg/L: 62% received antibiotics, in 47% evidence-based guidelines advised to prescribe antibiotics and in 53% evidence-based guidelines advised to withhold antibiotics

- of children testing negative on the clinical decision tree with CRP <5 mg/L: 11% received antibiotics, in 10% evidence-based guidelines advised to prescribe antibiotics and in 90% evidence-based guidelines advised to withhold antibiotics
- of children testing negative on the clinical decision tree with CRP ≥5 mg/L: 38% received antibiotics, in 23% evidence-based guidelines advised to prescribe antibiotics and in 74% evidence-based guidelines advised to withhold antibiotics

If a **diagnostic algorithm** including the **clinical decision tree, POC CRP test and safety netting advice** is provided, we can prudently assume to expect antibiotic prescribing rate in all children to be reduced to **22.65%** in the intervention arm, based on our systematic review (Verbakel et al., BMJ Open 2019), the previous trials in acutely ill children and a previous systematic review in adults.

For each of the outcomes stated above the following target difference is important for the key stakeholder groups consulted (e.g. patients, clinician, and healthcare funder): from 30.43% to 22.65%.

Using a 5% significance level (alpha 0.05), an intracluster correlation coefficient (ICC) of 0.063 (based on data from the ERNIE2 study in the exact same population), and power of 90% (beta 0.1), this would require **55 clusters of 50 patients** in both arms, resulting in **5500 children**. Drop-outs are unlikely to be a large problem since there will be only 1 study visit complemented by the collection of follow-up information. Imputation of missing values for patient- and/or parent/legal guardian-reported outcomes (if there are any) will be considered. Other outcomes will be collected in the patient health record of the physician.

R code:

We used the n4props-function in the R package CRTSize, using the following command:

n4props(0.3043,0.2265,50,0.063, alpha = 0.05, power=0.9, AR=1, two.tailed=TRUE, digits=3)

Considering the pragmatic nature of this trial and in correspondence with the 10% of practices performing non-consecutive inclusion of patients (high risk of selection bias) during the ERNIE2 trial, we will perform sensitivity analyses only considering physicians who have recruited a minimum of 10 patients per year. Taking into account the required sample size for this analysis of the primary study outcome as part of the sensitivity analysis, these assumptions result in a **total sample size of 6111 patients for the primary study outcome**.

Secondary outcomes

To demonstrate non-inferiority in the effect of the diagnostic algorithm including the **clinical decision tree, POC CRP test and safety netting advice** on the **secondary outcomes**, we use the following assumptions (based on observed proportions in previous trials in children) (11,27):

Secondary outcome	**Proportion in intervention group**	**Proportion in usual care group**	**Means + pooled standard deviation (SD)**	**Clinically significant change***
1. Time to clinical recovery (days)	NA	NA	Mean intervention group: 4.06 Mean usual care group: 4.15 Pooled SD: 3.89	1
2. Additional investigations at index and/or during follow-up (%)	9.0%	9.8%	NA	3%
3. Re-consultations during follow-up (%)	33%	34%	NA	4%
4. Antibiotic prescribing rate during follow up (%)	7%	8%	NA	2%

* based on consensus from a group of clinical researchers with experience in diagnostic and clinical research

NA: not applicable

The non-inferiority limit for the above 4 secondary outcomes is 1 day, 3%, 4%, and 2%, respectively, i.e. the intervention will be deemed non-inferior if the difference between the allocated groups (intervention – control) is less

than 1 day, 3%, 4%, and 2%, respectively. Therefore, the intervention will be deemed non-inferior if the upper limit of the 95% confidence interval lies below 1 day, 3%, 4%, and 2%, respectively.

Sample size for comparison of 2 means (for the first secondary outcome: time to full clinical recovery) and 2 proportions (for the other three secondary outcomes) for a non-inferiority trial was calculated with the following assumptions:

- 1-β = 0.80
- Allocation ratio (intervention/usual care) = 1
- Design effect (DE) = 1 + ρ(n-1)
- n = number individuals per cluster
- ρ = intracluster correlation coefficient
- We account for the clustering at the level of the individual physician
- n = 50 patients per cluster
- ρ = 0.025 (Previous studies have illustrated that in primary care ICCs for clinical outcomes are lower than those for process outcomes and the ICC for adverse effects to be around 0.025)(28)
- Resulting DE = 2.225
- to account for multiple testing (n=4), we have applied the Bonferroni-Holm correction, generally considered to be a rather conservative approach to control the family-wise error rate.(29) Therefore, our significance levels for the 4 secondary outcomes were 0.0125 (α/4), 0.167 (α/3), 0.025 (α/2), and 0.05 (α/4), respectively.

Secondary outcome	Preliminary sample size	Significance level (α)	Design effect (DE)	Total sample size (preliminary sample size * DE) for this outcome
1. Time to clinical recovery (days)	575	0.0125	2.225	1280
2. Additional investigations at index and/or during follow-up (%)	2079	0.0167	2.225	4626
3. Re-consultations during follow-up (%)	2312	0.025	2.225	5144
4. Antibiotic prescribing rate during follow up (%)	1906	0.05	2.225	4240

Taking into account the required sample size for these analyses of the primary study outcome and the secondary outcomes, aiming to recruit a **total sample size of 6111 patients** will be sufficient. Considering we previously recruited 8962 and 3981 acutely ill children in Belgium, this seems feasible.

11.1.2 impact of Covid on the primary outcome and revised sample size calculation during the trial

The S62005 ARON trial was planned before the COVID-19 pandemic. Though, the trial actually started in the initial part of the pandemic, just as the Delta variant (second wave) was first emerging: early 2021. The ARON trial kept going through all subsequent COVID-19 waves and is currently still ongoing.

The COVID-19 pandemic has shown that antibiotic prescribing has (for the better) declined during the pandemic, as shown by several studies and reports:

- Gillies, MB, Burgner, DP, Ivancic, L, et al. Changes in antibiotic prescribing following COVID-19 restrictions: Lessons for post-pandemic antibiotic stewardship. *Br J Clin Pharmacol*. 2022; 88(3): 1143- 1151.
- https://www.ecdc.europa.eu/en/news-events/reported-decrease-antibiotic-consumption-across-eueea-during-covid-19-pandemic
- Colliers, A.; De Man, J.; Adriaenssens, N.; Verhoeven, V.; Anthierens, S.; De Loof, H.; Philips, H.; Coenen, S.; Morreel, S. Antibiotic Prescribing Trends in Belgian Out-of-Hours Primary Care during the COVID-19 Pandemic: Observational Study Using Routinely Collected Health Data. Antibiotics 2021, 10, 1488. https://doi.org/ 10.3390/antibiotics10121488

This has urged us to revise our sample size calculation, based on the overall prevalence found in the first patients recruited, given the start of our trial during the pandemic.

This amendement concerns a clarification of the impact the COVID-19 pandemic has had on recruitment as well as the overall prevalence of our primary outcome, the antibiotic prescribing rate in children.

AIMS

With this amendment, we aim to:

- (1) investigate the influence of the COVID-19 pandemic on antibiotic prescribing rates in practices included in the ARON trial and (2) redetermine the required sample size for the ARON trial.
- (3) monitor whether inclusions were done consecutively, as per the study protocol, in order to minimize selection bias.

METHODS

1. Audit of antibiotic prescribing rate before and during the COVID-19 pandemic

An audit is an official methodical examination and review, typically of an organisation's or individual's accounts or financial situation[1]. In the context of this appendix, we aim to audit practices' antibiotic prescribing rates in a time-matched before-after manner. We will compare the rate before the COVID-19 pandemic (before, Figure 1) and during the COVID-19 pandemic (after, Figure 2), in an identical period during the year (Figure 1). A statistically significant change from baseline quantified by odds ratios will indicate a change in antibiotic prescribing behaviour due to COVID-19. This audit will be executed by the study coordinator (SC) that manages the practice.

The audit questions are presented in Figure 7 and Figure 8.

ARON 1.Jaar 2018: alle kinderen 6maanden – 12 jaar die een contact hebben gehad bij de huisarts. a.Over hoeveel kinderen ging het

Contact	Type	Is gelijk aan	Consultatie
Contact	Auteur	Is gelijk aan	[redacted]
Patiëntenadministratie	Geboortedatum	Is kleiner dan of gelijk aan	30/06/2017
Contact	Datum	Is groter dan of gelijk aan	01/01/2018
Contact	Datum	Is kleiner dan of gelijk aan	31/12/2018
Patiëntenadministratie	Geboortedatum	Is groter dan of gelijk aan	01/01/2006

ARON 1.Jaar 2018: alle kinderen 6maanden – 12 jaar die een contact hebben gehad bij de huisarts b.Hoeveel kinderen hebben minstens 1 AB voorschrift gekregen (matched 1 mei 2017 t/m 30 nov 2018)

Patiëntenadministratie	Geboortedatum	Is groter dan of gelijk aan	01/05/2005
Contact	Type	Is gelijk aan	Consultatie
Patiëntenadministratie	Geboortedatum	Is kleiner dan of gelijk aan	31/12/2016
Contact	Datum	Is kleiner dan of gelijk aan	30/11/2018
Contact	Datum	Is groter dan of gelijk aan	01/05/2017
Contact	Auteur	Is gelijk aan	[redacted]
Medicatie	Datum	Is kleiner dan of gelijk aan	30/11/2018
Medicatie	BCFI boom	Is gelijk aan	Antibacteriële middelen
Medicatie	Datum	Is groter dan of gelijk aan	01/05/2017

Figure 7. Audit questions (before start of the trial) in CareConnect software (Corilus).

[1] Merriam-Webster dictionary. https://www.merriam-webster.com/dictionary/audit. Accessed 9 January 2023.

ARON 2.En de periode dat ze gerekruteerd hebben tijdens de trial (gemakkelijk te vinden in Redcap fictief voorbeeld 1 mei 2021 t/m 30 november 2022). a.Over hoeveel kinderen ging het

Patiëntenadministratie	Geboortedatum	Is kleiner dan of gelijk aan	30/11/2020
Patiëntenadministratie	Geboortedatum	Is groter dan of gelijk aan	01/05/2009
Contact	Auteur	Is gelijk aan	[redacted]
Contact	Type	Is gelijk aan	Consultatie
Contact	Datum	Is groter dan of gelijk aan	01/05/2021
Contact	Datum	Is kleiner dan of gelijk aan	31/10/2022

ARON 2.En de periode dat ze gerekruteerd hebben tijdens de trial (gemakkelijk te vinden in Redcap - bv 1 mei 2021 t/m 30 november 2022). b.Hoeveel kinderen hebben minstens 1 AB voorschrift gekregen

Medicatie	BCFI boom	Is gelijk aan	Antibacteriële middelen
Contact	Datum	Is kleiner dan of gelijk aan	31/10/2022
Patiëntenadministratie	Geboortedatum	Is kleiner dan of gelijk aan	30/11/2020
Contact	Datum	Is groter dan of gelijk aan	01/05/2021
Medicatie	Datum	Is groter dan of gelijk aan	01/05/2021
Patiëntenadministratie	Geboortedatum	Is groter dan of gelijk aan	01/05/2009
Contact	Auteur	Is gelijk aan	[redacted]
Contact	Type	Is gelijk aan	Consultatie
Medicatie	Datum	Is kleiner dan of gelijk aan	31/10/2022

Figure 8. Audit questions (after start of the trial) in CareConnect software (Corilus).

Most software packages, e.g., CareConnect[2], Daktari[3], HealthOne[4], of which the former dominate the market, have a statistics/search module. This allows for easy and uniform access to the required data.

2. Sample size calculation

The original sample size calculation was based on previous data, assuming an overall prescribing rate of 26.5% in those children recruited for our trial.

The overall prevalence was found to be 18% overall in children recruited in the first 4938 patients recruited in the ARON trial.

If we were to assume a reduction of 5.3% (proportionate to our original reduction) between the usual care group and the intervention group, using a 5% significance level (alpha 0.05), an intracluster correlation coefficient (ICC) of 0.063 (based on data from the ERNIE2 study in the exact same population), and power of 90% (beta 0.1), this would require **63 clusters of 50 patients** in both arms, resulting in **6300 children**.

R code:

We used the n4props-function in the R package CRTSize, using the following command:

n4props(0.2065,0.1435,50,0.063, alpha = 0.05, power=0.9, AR=1, two.tailed=TRUE, digits=3)

Considering the pragmatic nature of this trial and in correspondence with the 10% of practices performing non-consecutive inclusion of patients (high risk of selection bias) during the ERNIE2 trial, we will perform sensitivity analyses only considering physicians who have recruited in a consecutive way. Taking into account the required sample size for this analysis of the primary study outcome, these assumptions result in a **total sample size of 7000 patients for the primary study outcome**.

3. Non-consecutive recruitment

In the protocol, we have specified: "The participating physicians will be asked to consecutively recruit children with an acute illness over the recruitment period covering two winter seasons."

We wanted to further clarify what is meant by non-consecutive recruitment, by stating that GPs are likely to breach this assumption if:

- They recruit less than 10 patients per year

[2] CareConnect General Practitioner, Handleiding, Extra/tandwiel, Statistiek. https://careconnectmanual.corilus.be/nl/node/98. Accessed 10 January 2023.

[3] Daktari gebruikersandleiding, "5.4 Geavanceerd zoeken". https://www.daktari.be/files/Daktari-handleiding.pdf. Accessed 10 January 2023.

[4] HealthOne, Basis Handleiding. https://www.dropbox.com/s/4fwlwvr56z0wlw8/Basis%20handleiding.pdf?dl=0. Accessed 10 January 2023.

- They perform a point-of-care CRP test on nearly all (>90%) of the included children
- They deliberately only include children (>90%) that do not need antibiotics and exclude those that might need antibiotic treatment.

All of the above circumstances introduce significant selection bias and reduce the generalisability of our findings. Although we plan to perform an intention-to-treat analysis given the pragmatic nature of our trial, protocol violations caused by the inappropriate inclusion/exclusion of patients will be far more detrimental for the validity of our trial. Apart from the intention-to-treat analysis a per protocol sensitivity analysis will be performed.

The abovementioned assumptions can be tested, based on:

- the qualitative sub-study (semi-structured interviews with parents and physicians) in a selection of the recruiting practices
- the audit as described above
- monitoring visits by the clinical trial centre supporting data monitoring of the ARON trial

11.2 Planned recruitment rate

Our groups have successfully completed a range of trials in both children and adults with acute illnesses in primary care.

The same primary care network used in previous studies by the sponsors group will be used for recruitment, previously resulting in sample sizes of up to 8962 children.

The planned recruitment period will be 21 months. Taking into account an inclusion rate of 1 in 5 of all eligible children, we will include a total of 122 ambulatory care physicians.

11.3 Statistical analysis plan

11.3.1 Summary of baseline data and flow of patients

Presentation of baseline characteristics of the study population and comparability of the 2 arms will be based on the following variables:

- Age (median and 25-75 percentiles)
- Gender (percentage)
- Ethnicity (percentages)
- Parental smoking status (percentage)

Differences in baseline characteristics and clinical features will be analysed through Chi-squared testing and nonparametric equality-of-medians testing to assess potential recruitment bias.

11.3.2 Primary outcome analysis

The primary endpoint will be analyzed according to the intent-to-treat (ITT) approach.

We will use a mixed-effects logistic regression analysis to account for the clustering at practice level, and other potential interaction terms, such as the child's age.

Multiple imputation will be applied to deal with missing data. Imputation will be performed for the binary outcome variable and logistic regression will be used as imputation model. Predictors for the imputation model are baseline patient characteristics and intervention.

Subgroup analysis will be performed in order to investigate how the primary outcome behaves in function of:

- age categories
- gender

11.3.3 Secondary outcome analysis

We will use a mixed-effects logistic regression analysis to account for the clustering at practice level, and other potential interaction terms, such as the child's age.

Multiple imputation will be applied to deal with missing data. Imputation will be performed for the binary outcome variable and logistic regression will be used as imputation model. Predictors for the imputation model are baseline patient characteristics and intervention.

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

Drop-outs are unlikely to be a large problem since there will be only 1 study visit complemented by the collection of follow-up information.

We will analyze the whole population for the primary analysis and perform a sensitivity analysis excluding the low recruiting practices (less than 10 patients recruited during 12 months) to avoid our results to be susceptible to selection bias. In previous trials this resulted in approximately 5% of practices who did not contribute to these sensitivity analyses as the risk of selection bias was deemed extremely high in these practices.

Practices that do not recruit children at all will be stopped after the first two monitoring visits and replaced by new practices to avoid reducing the total number of clusters, available for analysis.

See section 8.6 for strategies to maximize follow-up and to prevent missing data. See sections 11.3.2 and 11.3.3 for statistical handling of missing data.

The percentage of missing data for the primary outcome measure of antibiotic prescribing rate is expected to be low as this will be registered at the first-contact consultation. In our previous trial, we found 4% of missing data for the primary outcome of antibiotic prescribing rate. Multiple imputation will be considered for the primary outcome measure as well as missing values for patient-reported outcomes (if there are any). Other outcomes will be collected in the patient health record of the physician.

11.4 Data collection for economic evaluation

One of the goals of the KCE Trials programme is to improve the efficiency of the healthcare system. This protocol has been designed with a later possible economic analysis in mind. The planned economic analysis is briefly described below, together with the variables collected in this protocol for this purpose. For the sake of clarity, the economic analysis is not a part of this trial. The decision to conduct such economic analysis will depend on the effectiveness results of this trial.

OVERVIEW

The first part is a cost study with the aim to identify significant cost drivers and to compare the cost impact of the intervention with its alternative 'usual care'. A cost driver is a component in the health service significantly associated with the costs. The potential subcategories of costs considered are: acute outpatient, acute inpatient, primary care, residential care, pharmacy prescriptions, chronic prescriptions, diagnostic tests, visit to A&E, intervention costs.(30) A health care payer perspective is adopted and includes payments out of the federal government's and the communities' health care budget as well as patients' co-payments.

The second part on the economic evaluation concerns cost-consequences analysis, comparing costs and consequences (expressed in hospitalizations, consultations, pharmaceuticals (re-imbursed and non-reimbursed) and productivity) and cost-utility-analysis (CUA) using broader metrics such as QALYs, between participants in the 'intervention' study group (intervention group) and those in the 'usual care' study group (control group). The goal of this analysis is to indicate the technical and allocative efficiency (cost per effect) of the intervention and care as usual.

ANALYSES

<u>Part I: cost estimations</u>

In both study groups (with about N=3056 in every group), the subcategory costs (pharmaceuticals, consultation, hospitalization, productivity) and total costs per patient will be calculated. These costs include : the direct medical costs of healthcare use for which a nomenclature code exist and which will be tracable in the datasets that we will have access to (see also below) and the cost of the intervention itself (the POC testing), and: the indirect costs for patients (e.g. caregiver time, cost of absenteeism and presenteeism, administrative costs). In addition, between-group differences are calculated for each subcategory and total costs. First, descriptive statistics will provide

unadjusted information on the magnitude and distribution of the 'intervention' costs for each of the subcategories compared to the 'usual care' group. Secondly, generalized linear modelling (GLM) will be applied to evaluate the total costs between both groups adjusted for the other independent factors (patient characteristics, cluster, etc).

Part II: health economic evaluation (CUA) Bottom-up approach:

In this phase, an analysis of the costs and health effects alongside the clinical trial will be conducted. The effects will be expressed broadly as consequences (e.g. hospitalizations or cases avoided) but also as 'utilities' (i.e. a health-related quality of life weight, range from 0 [dead] to 1 [perfect health], i.e. QALYs).

For both study groups, resource use data and health-related quality of life (HRQOL) data will be collected during the trial using information from the patients' health records and using a questionnaire (self-reported) as part of the smartphone app for parents for those resources not captured by the health records. Simultaneously, information from the RIZIV nomenclature database will be used to attach costs to the different resource use data. Alongside the data collected from the app during the trial, the costs associated with hospitalisation, consultations, pharmaceuticals (re-imbursed) during follow-up will be collected by linking the national insurance number (collected during the index consultation by the participating physician) of children via a trusted third party to the administrative databases reporting on healthcare usage. The HRQOL data will be collected using the proxy version of the EQ-5D-Y questionnaire (24) (filled out at regular timings by the participants (by parents). As we anticipate a large proportion of our study population to be below the age of 4 years, we will include additional scales aiming to assess quality of life or rather pain as this is assumed to be the main driver for quality of life in the young infants and has shown to have face validity:

- The Wong Baker FACES Pain Scale (25), which has been validated in children from 3 years to 18 years of age (31)
- The FLACC scale (26), which has been validated in children from 0 to 18 years of age (32)

Resource use data will be collected during follow-up by linking the national insurance number to the administrative healthcare usage databases, as well as from the data collected in the parental app (hospitalization, consultation). This complementary approach is preferred to avoid missing data and assess representativeness of our analysis.

Health-related quality of life data will be collected at regular time points: at day 1, day 4, and day 7 for all children and each week thereafter for children that have not recovered after day 7 (maximum up to day 28).

Information related to the intervention costs will be collected in the nested qualitative study, including the physician's time spent on the program (as reported by the participating physicians in the nested qualitative substudy). The latter costs will be recalculated at patient level.

The ratio of the incremental costs to the incremental effects is called the incremental cost-effectiveness ratio (ICER) calculated as: $(Cost_N - Cost_C)/(Health\ effect_N - Health\ effect_C)$a. This measure reflects the difference in costs per unit of effect. We will calculate ICERs in terms of natural effects (number of packages AB prescribed) and in terms of QALYs, or net benefits (in case of dominated or dominant interventions).

A well-known issue is the presence of missing data related to the different outcome variables (cost data). Different methods exist to handle this. In the current research project, single imputation methods will be used. In this method, the missing data are replaced with a single predicted value (e.g. the adjusted mean value).(33) Sensitivity analyses will be conducted to determine how different input values will impact the outcome.(33)

Decision-analytic model will be used to predict longer-term patient outcomes and complications for patients as well as their economic impact in the 'intervention' arm versus the 'usual care' arm, as well as to investigate the effect of changes in particular parameters (sensitivity analysis). We will use a combination of decision-trees and markov models to follow hypothetical cohorts over time. The main data as input for the model will be the occurrence of hospital admission for serious infection, health outcomes for non-hospitalized patients and reported cost and HRQoL data (obtained from phase 1 and in case needed from published literature). This kind of model allows us to simulate transitions in various health states beyond the duration of the intervention, and as each health state is associated with costs and utilities, to estimate cost-effectiveness ratios. The health effects in this model will be mainly expressed as quality-adjusted life years (QALYs). QALYs are calculated by multiplying the utility level (information obtained in phase 1) with the number of years and individual lives with the condition.

Health economic evaluation studies are frequently characterized by degrees of uncertainty or methodological considerations. In the current study, one-way, multi-way and probabilistic (monte carlo/non-parametric bootstrapping) sensitivity analyses will be conducted to handle various uncertainties. Uncertainty analyses will be expressed in terms of cost-effectiveness acceptability curves.

12 DATA HANDLING

12.1 Data collection tools and source document identification

Data collection will be performed through REDCap, an electronic data capture software. This tool allows for secure, encrypted and pseudonomysed data transfer from multiple sources into a central database. Data can be collected continuously or in a one-time fashion depending on the resource. REDCap is a secure web application for building and managing online databases. REDCap is specifically geared to support online data capture for research studies.

12.2 Data handling and record keeping

REDCap stores its data and all system and project information in various relational database tables (i.e. utilizing foreign keys and indexes) within a single MySQL database. All project data is stored and hosted at our institution, and no project data is ever transmitted at any time by REDCap from our institution to another institution or organization.

12.3 Access to Data

REDCap has a built-in audit trail that automatically logs all user activity and logs all pages viewed by every user, including contextual information (e.g. the project or record being accessed). Whether the activity be entering data, exporting data, modifying a field, running a report, or add/modifying a user, among a plethora of other activities, REDCap logs all actions. The logging record can itself be viewed within a project by users that have been given privileges to view the Logging page. The Logging page allows such users to view or export the entire audit trail for that project, and also to filter the audit trail in various ways based upon the type of activity and/or user. The built-in audit trail in REDCap allows administrators to be able to determine all the activity and all the data viewed or modified by any given user.

12.4 Archiving

The Sponsor is responsible for archiving study specific documentation (such as but not limited to protocol, potential amendments and final report) for at least twenty years. Destruction of essential documents will require authorization from the Sponsor.

13 MONITORING, AUDIT & INSPECTION

The investigator will permit trial-related monitoring, and audits, providing direct access to all related documents.

Electronic CRFs, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor and auditor. The accuracy of the data will be verified by review of these documents.

For all details about monitoring, we would like to refer to the Trial Monitoring Plan, which will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Ethics Committee (EC) review & reports

The study will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol, the informed consent forms and other related documents e.g. advertisements and physician information letters, will be submitted for review to the Research Ethics Committee (REC) and to the Sector Committee for Social Security and Health of the Privacy Commission.

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

The study can and will be conducted only on the basis of prior informed consent by the parents or legal guardian of the study participants, to participate in the study. Extensive discussion of risks and possible benefits of participation will be provided to the patients and/or their families. The participating physician shall obtain a signed informed consent form for all study participants prior to their enrolment and participation in the study in compliance with all

applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The research facility shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

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

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

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

14.2 Peer review

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

14.3 Public and Patient Involvement

We will present the suggested intervention to parents and children to receive input on potential barriers and facilitators of our proposed trial.

Furthermore, patient representative groups will be contacted to obtain useful feedback regarding our trial.

As we are currently involved in several paediatric studies, we are in the process of setting up a standing patient panel to advise on all ongoing projects. This would encompass:

- communicating and engaging with parents through co-design workshops at the pilot phase to ensure that research process accurately address the needs of the parents
- individual interviews with the parents will be carried out alongside the trial to ensure that the research outputs reflect the underpinning barriers and facilitators to intervention uptake, increasing their opportunity to benefit.
- we will ask them to assess any patient facing material that will be produced, such as patient information sheets, and ask for their feedback on readability and content.
- we will also ask for advice on how to disseminate our findings to a lay audience.
- the principal investigator will be appointed PPI co-ordinator and will liaise with the group during study set up, recruitment and dissemination phases.
- they will be reimbursed for their time, travel and childcare expenses.
- the PI will make sure the results of the panel discussion will be passed on to the steering committee of the study.

14.4 Regulatory Compliance

This protocol and other related documents will be submitted for review to the Sector Committee for Social Security and Health of the Privacy Commission.

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

14.5 Protocol compliance

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

It is acknowledged and agreed that prospective, planned deviations or waivers to the protocol are not allowed under applicable regulations on clinical studies and must not be used. However, should there be an accidental protocol deviation, such deviation shall be adequately documented on the source documents and on the relevant forms and

reported to the Chief Investigator and Sponsor immediately. Protocol deviations which are found to frequently recur, will require immediate action. Chief Investigator acknowledges that such recurring protocol breaches could be potentially classified as a serious violation (as defined under section 13.6).

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

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

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

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

14.7 Data protection and patient confidentiality

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

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

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

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

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

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

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

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

14.9 Indemnity

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

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

14.10 Access to the Study Data by KCE and similar institutes in the EU

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

A distinction is to be made by access by KCE (and similar institutes in Europe) and access by other parties.

Access to Study Data by KCE is fully defined in the contract between KCE and the Sponsor and the research agreement template is publicly available on the KCE website. Link: https://kce.fgov.be/en/resources-for-investigators

14.11 Access to the final trial dataset by other parties

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

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

15 DISSEMINATION POLICY

15.1 Dissemination policy

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

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

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

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

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

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

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

We will ensure that the findings of the study will be disseminated to relevant stakeholders other than the scientific world including the general public, health care providers and policy makers. Therefore, information about the study will be spread through websites (news sites of the universities, medical and health information sites such as gezondheid.be), newsletters and press releases. Next, we will inform agencies such as BAPCOC, insurance

companies and patient representative groups (Vlaams Patiënten Platform, LUSS) and encourage them to further circulate the information through their own communication channels. Furthermore, the results will be presented to various government bodies and policy makers and on conferences and on local seminars for general practitioners (LOKs, GLEMs). Finally, the study findings will be published in national journals (for example HANU, Revue de la Médicine Générale).

In case this study proves our diagnostic algorithm to be more effective than usual care to reduce antibiotic prescribing rate in children, translating this evidence into routine practice will be the next great challenge.

Though the development of an implementation strategy is clearly beyond the scope of this study, we would like to formulate some general recommendations/considerations.

- the implementation intervention strategy should be developed based upon a theoretical framework applying a systematic approach (Vis 2015). Multiple theories and frameworks exist but one common ingredient comprises an in-depth analysis of the perceptions, barriers and facilitators as experienced by all stakeholders. The process evaluation that is part of this trial will be informative in respect to this and hence provide a basis for an implementation strategy.
- it will be essential to educate physicians about introducing the diagnostic algorithm including POC CRP testing and safety netting advice in their daily practice. This will require training which should be delivered through accredited Continued Medical Education (CME) but should also be part of the basic medical curriculum for physicians. The engagement of the majority of the Belgian academic centres for general practices in this trial will undoubtedly facilitate the integration of education about diagnosis and management of infectious diseases in children in ambulatory care –in combination with antibiotic prescribing guidelines- in the medical curriculum.

15.2 Authorship eligibility guidelines and any intended use of professional writers

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

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APPENDICES

APPENDIX 1. RISK ASSESSMENT OF THE TRIAL INTERVENTION(S)

Risks associated with trial interventions

☒ A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):

The risk of adverse events occurring as a consequence of the intervention in this trial is unlikely therefore safety reporting will be limited to the safety reporting that is necessary in routine care

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

Outline any processes (e.g. IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach.