belgian pediatric clinical research network

Pediatric clinical trials:
opportunities, challenges and pitfalls (BPCRN within C4C)

Johan Vande Walle

Laura Persijn, Sevasti Karamaria, Ann Raes, Daphné Christiaens, Lieve Nuytinck, Eva Degraeuwe

COI

- Many of my patients
  - Because of lack of drugs
  - Because of lack of knowledge how to use the drug
- Story of an adolescent dying
  - When the drug was already available in France, but not yet reimboursed in Belgium.
  - If she would have participated in a clinical trial, she would still be alife
- Consultancies Bayer, Ferring, Astellas, Kyowa Kyrin, Alnylam

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PAEDIATRIC POPULATION: CHILDREN ARE NOT SMALL ADULTS :

- About 20% of the European population is < 18 years old.
  - epp.eurostat.ec.europe.eu
- 33% of all drugs in Europe are licensed for use in children.
  - Ceci et al. Eur J Clin Pharmacol 2006; 62:947-52
- Off label /or off –licence
  - 50% % in general paediatrics
    - t Jong et al. Pediatrics 2001;108: 1089-93
  - 90% of prescriptions in (neonatal) intensive
    - Conroy et al. BMJ 2000; 320: 79-82


Eur J Clin Pharmacol (2015) 71:1–13
DOI 10.1007/s00228-014-1768-9

REVIEW ARTICLE

Use of off-label and unlicenced drugs in hospitalised paediatric patients: a systematic review

Joana Magalhães · António Teixeira Rodrigues · Fátima Roque · Adolfo Figueiras · Amílcar Falcão · Maria Teresa Herdeiro

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PAEDIATRIC POPULATION: CHALLENGE /BURDEN

Availability of medicines for children:

- with well described therapeutic effect
- without (severe) adverse reactions
- in an age-appropriate formulation
- Through good quality clinical trials in children

Burden:

- Ethical issues
- High cost ↔ small market size
- Technical difficulties : sampling, few patients..need for many centers
- Heterogeneous group
- No track record for CTU's

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INTRODUCTION :

1. History and rationale
2. Conect4children : C4C ?
3. BPCRN = national network / national Hub
4. C4C project
5. Added value
6. Future perspectives

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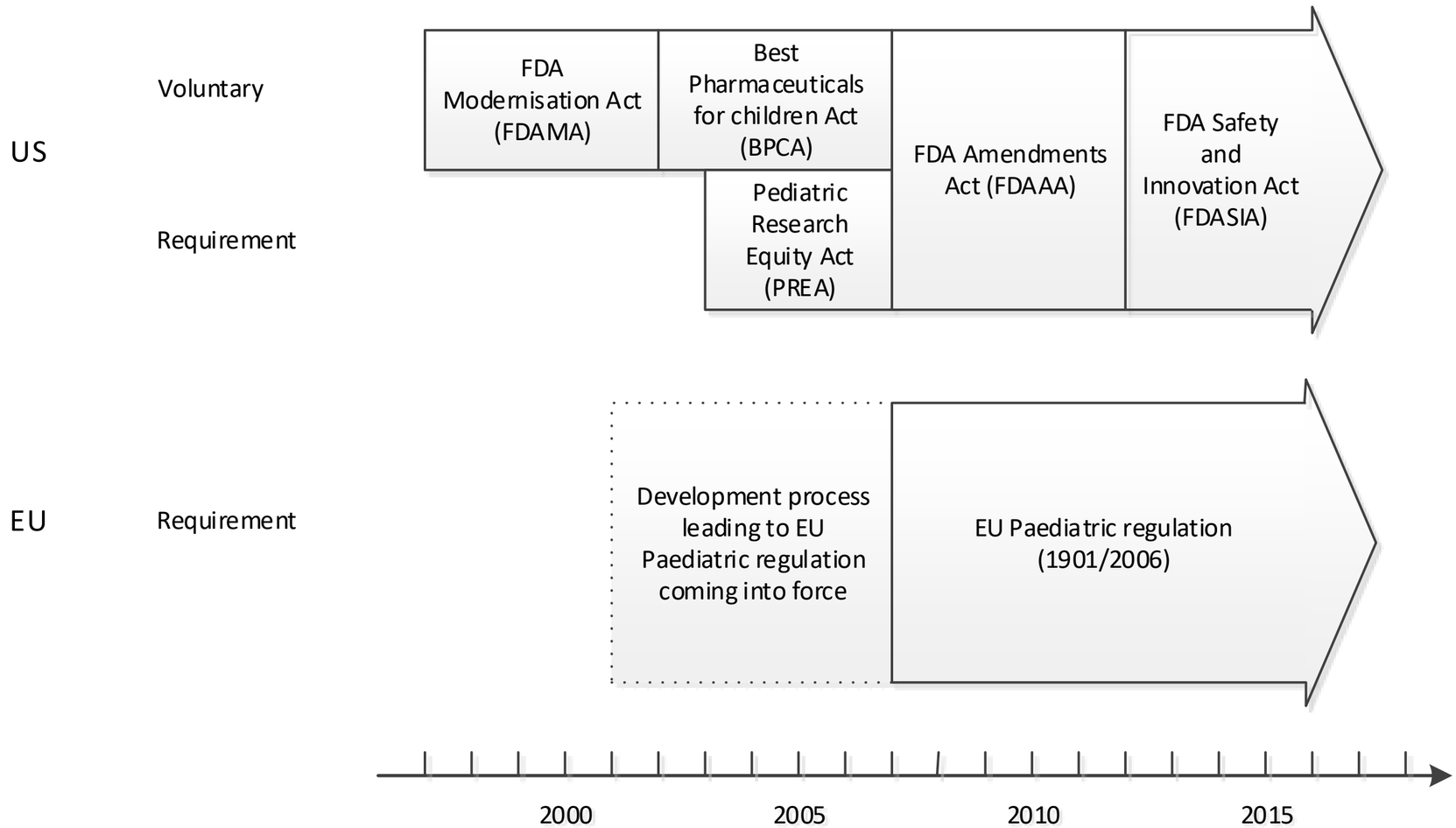
PAEDIATRIC MEDICINES INITIATIVES



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AUDIT OF FDA AND EMA REGULATIONS 2016

Majority of pediatric trials were not succesvol

1) Academic opinion
    1) Bottum up approach
    2) Need optimalisation study design
2) Analysis by pharma
    1) Failure
        1) to identify adequate patients and CT sites
        2) to perform HQ clinical trials
    2) Time losses for
        1) Feasibilities
        2) Contracting
        3) Time to first patient + 50% zero inclusion-rates

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SAFEPEDRUG : ACADEMIC CONSORTIUM, PRECLINICAL & CLINICAL NETWORK

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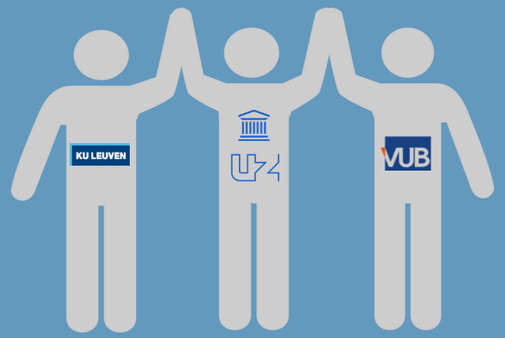

FWO-SBO
2014-2018

evolved into **clinical trial unit SAFEPEDRUG** and into the Belgian participation with the **European trial network conect4children (c4c)**

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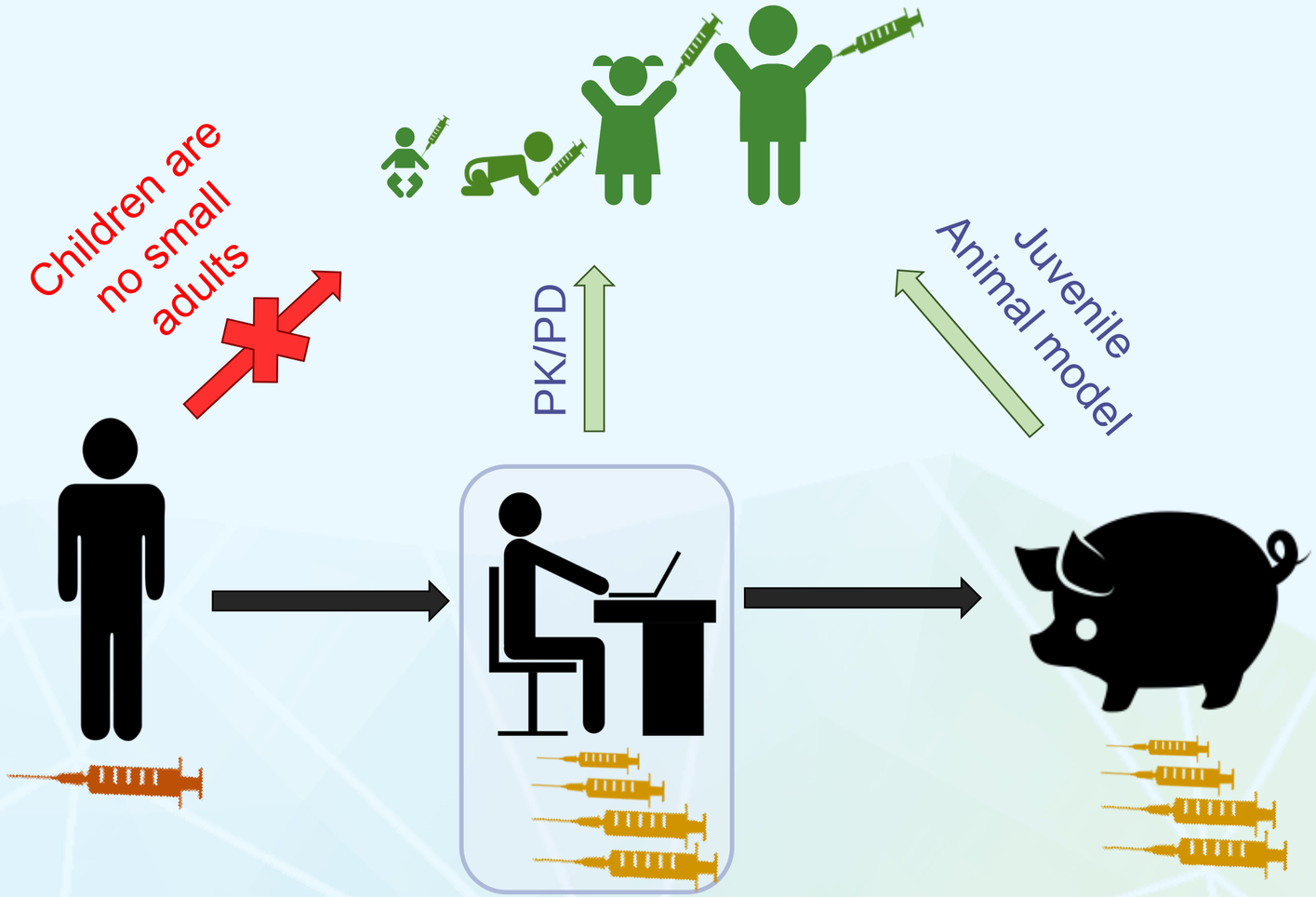

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ESDPP congress 2021 long oral presentation – *Degraeuwe et al. - conect4children in Belgium*

Goal: Improve paediatric drug development, age-appropriate dosage schemes and formulations to counteract off-label drug use.

4 therapeutics studied

AUDIT OF FDA AND EMA REGULATIONS 2016

Majority of pediatric trials were not succesvol

1) Academic opininion
    1) Bottum up approach
    2) Need optimalisation study design
2) Analysis by Pharma
    1) Failure to
        1) timely identify adequate patients and CT sites
        2) perform HQ clinical trials = infrastructure
    2) Major time losses for
        1) Feasibilities
        2) Contracting
        3) Time to first patient + 50% + zero inclusion-rates

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EUROPEAN COLLABORATION IN CLINICAL TRIALS

INNOVATIVE MEDICINES INITIATIVE

CONNECT FOR CHILDREN PROJECT

www.conect4children.org

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777389.
The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

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C4C

- 10 EFPIA Partners
- 20 EU National Hubs
- Over 250 sites for pediatric clinical trials

Until 2020: 6 large paediatric hospitals connected

KEY OBJECTIVES

- More efficient trial implementation through the set-up of **national hubs** and qualified sites
- Input in clinical trial design and implementation from **pilot expert advisory groups** and other fora
- **Educational programme** for health professionals and **awareness raising campaigns** for the general public
- Identification of **data standards** and **performance metrics**
- Business cases for **sustainability** beyond IMI funding

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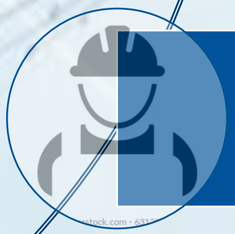
BACKGROUND OF BELGIAN NATIONAL CLINICAL TRIAL NETWORK : BPCRN

Initiated in 2009 by the Belgian Paediatric Society

The **SAFEPEDRUG** federal funded FWO (IWT 130033)

- Establishment of a paediatric clinical trial center, connected to the adult trial department D.R.U.G. at the **University Hospital Ghent.**

Coordinative center for **conect4children (c4c) in Belgium.**



Network non-c4c activities in subcontractorship (e.g. I-ACT for children)

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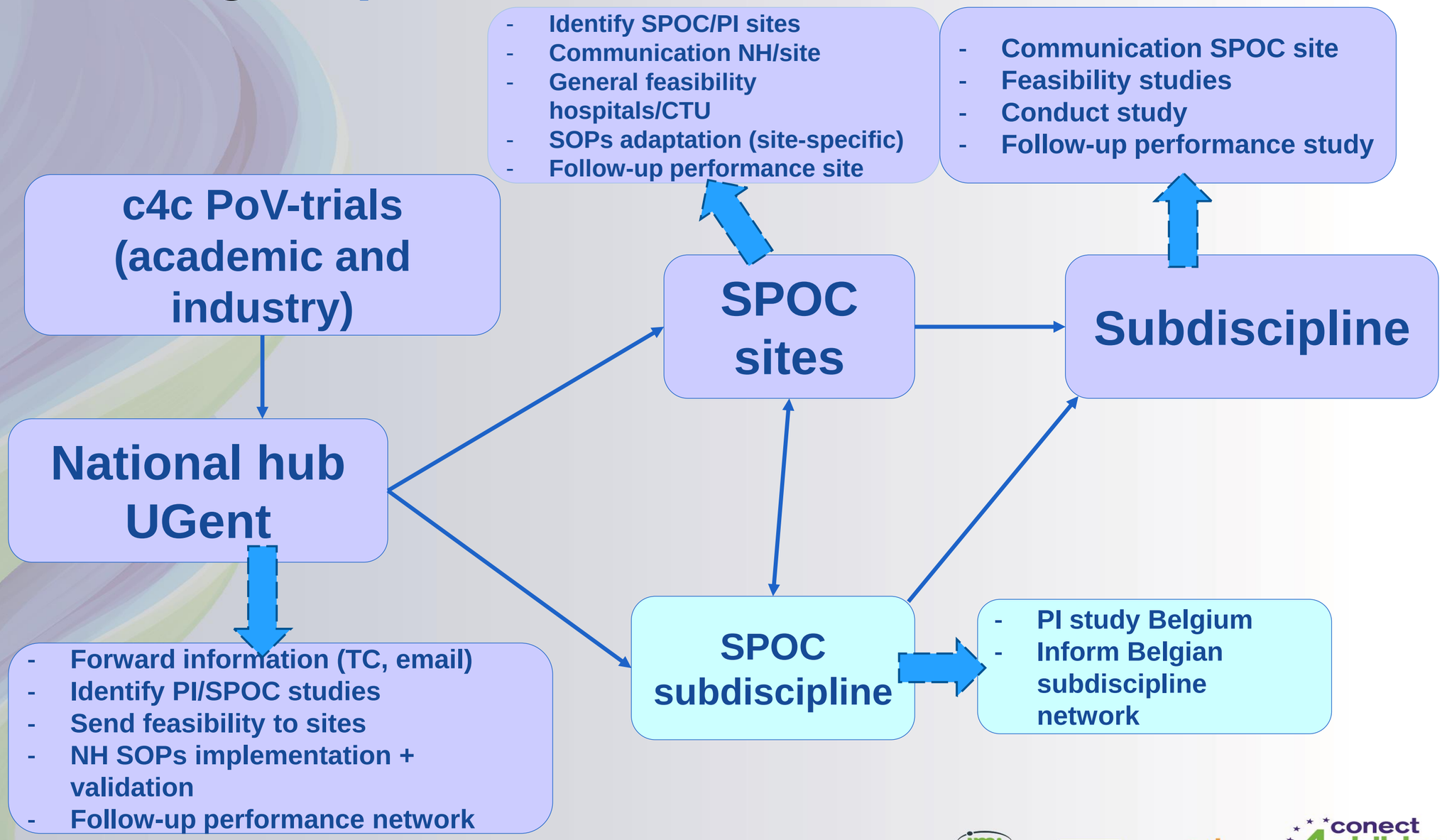
THE BPCRN STRUCTURE

1. Zee preventorium
2. AZ Sint-Jan Brugge
3. AZ Delta
4. AZ Groeninghe
5. UZ Gent / UGent (B. Nat. Hub)
6. UZ Antwerpen
7. ZNA Paola Ziekenhuis
8. Jessa Ziekenhuis
9. UZ Brussel
10. UCL
11. HUDERF
12. UZ Leuven
13. CHU Charleroi
14. Clinique CHC
15. CHU Liège

Belgian pediatric clinical research network



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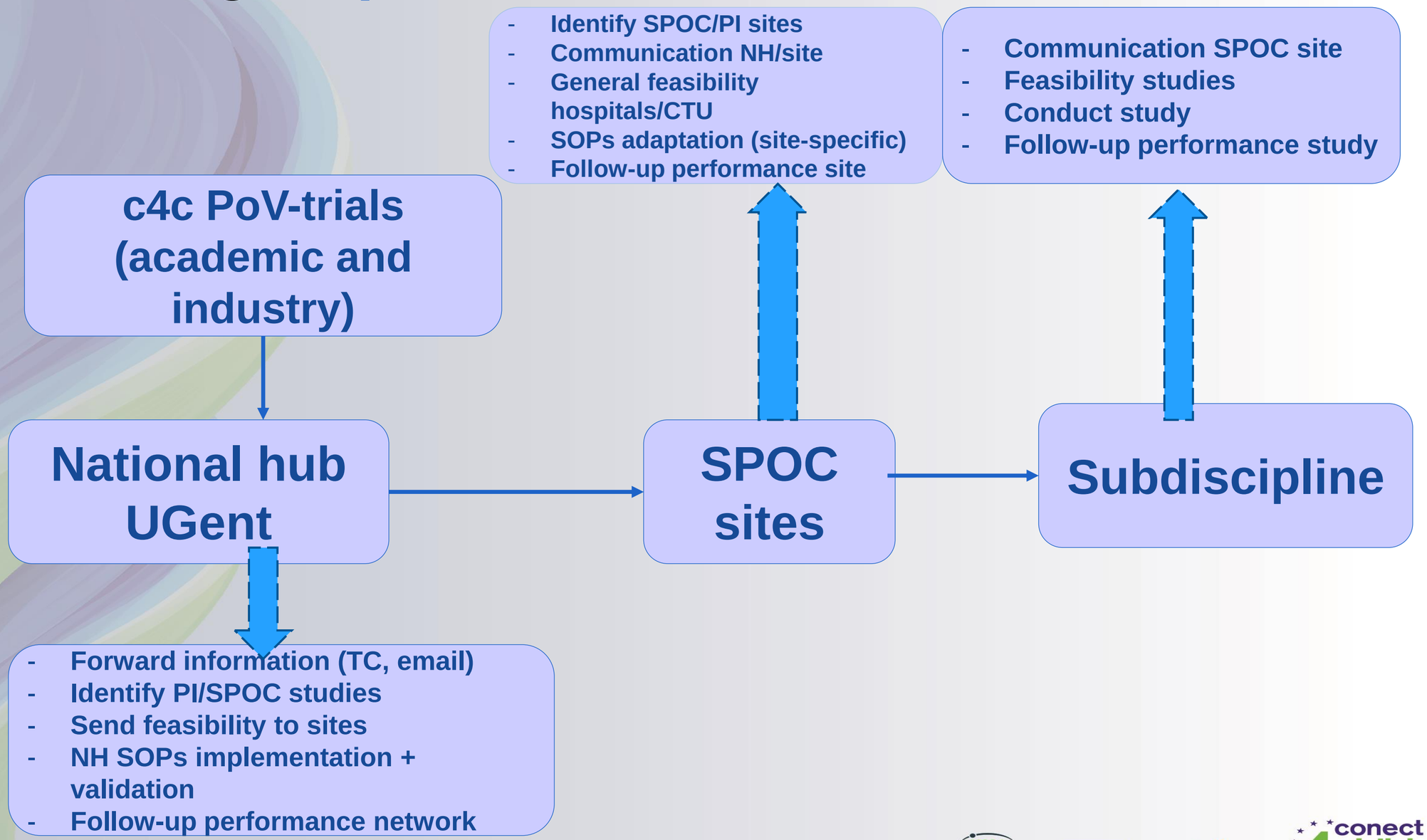
Belgian pediatric clinical research network



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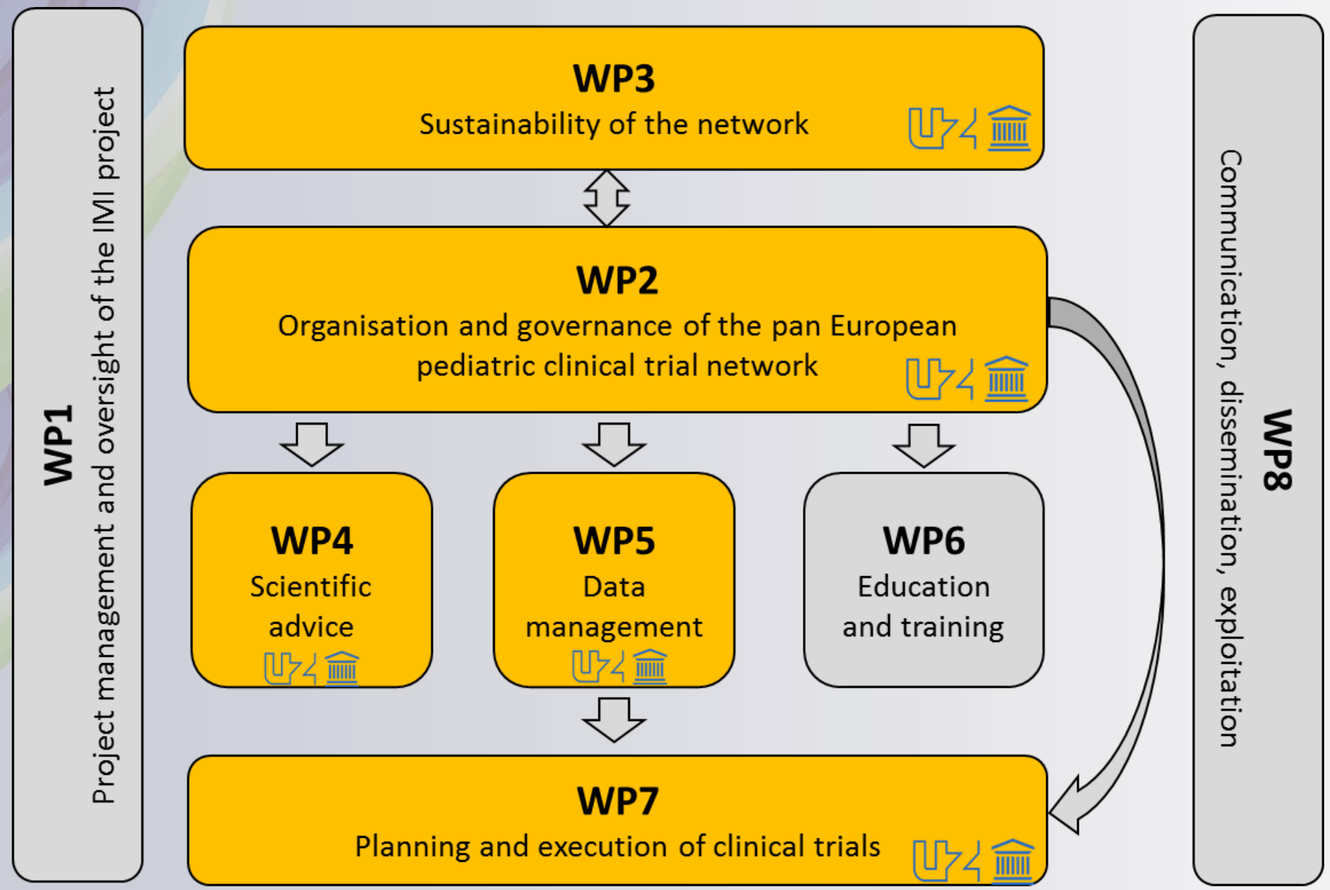
C4C WORK PACKAGES

Belgian NH (Ugent) is also involved in multiple WP to organise the European network



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C4C PROJECT : HOW C4C IS BEING TESTED

- Can C4C do better than the past?
- Evaluating **metrics** about start-up and conduct of studies
- Proof-of-viability trials: target 4 academic and 4 industry driven studies
  - 3 Non-industry-sponsored : initial target 4 (opening 2020)
    - Neonatology
    - Mucoviscidosis /infectiology
    - Kawasaki disease
    - Osteogenesis imperfecta : failed to initiate
  - 5 Industry sponsored (opening 2021): initial target 4
  - Multiple extra studies within C4
  - But also outside C4C = network of national networks (N3**)**

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SOPS TO BE SHARED

- Pharmacovigilance
- Compliance
- Education and training
- Metrics
- Quality
- IMP management

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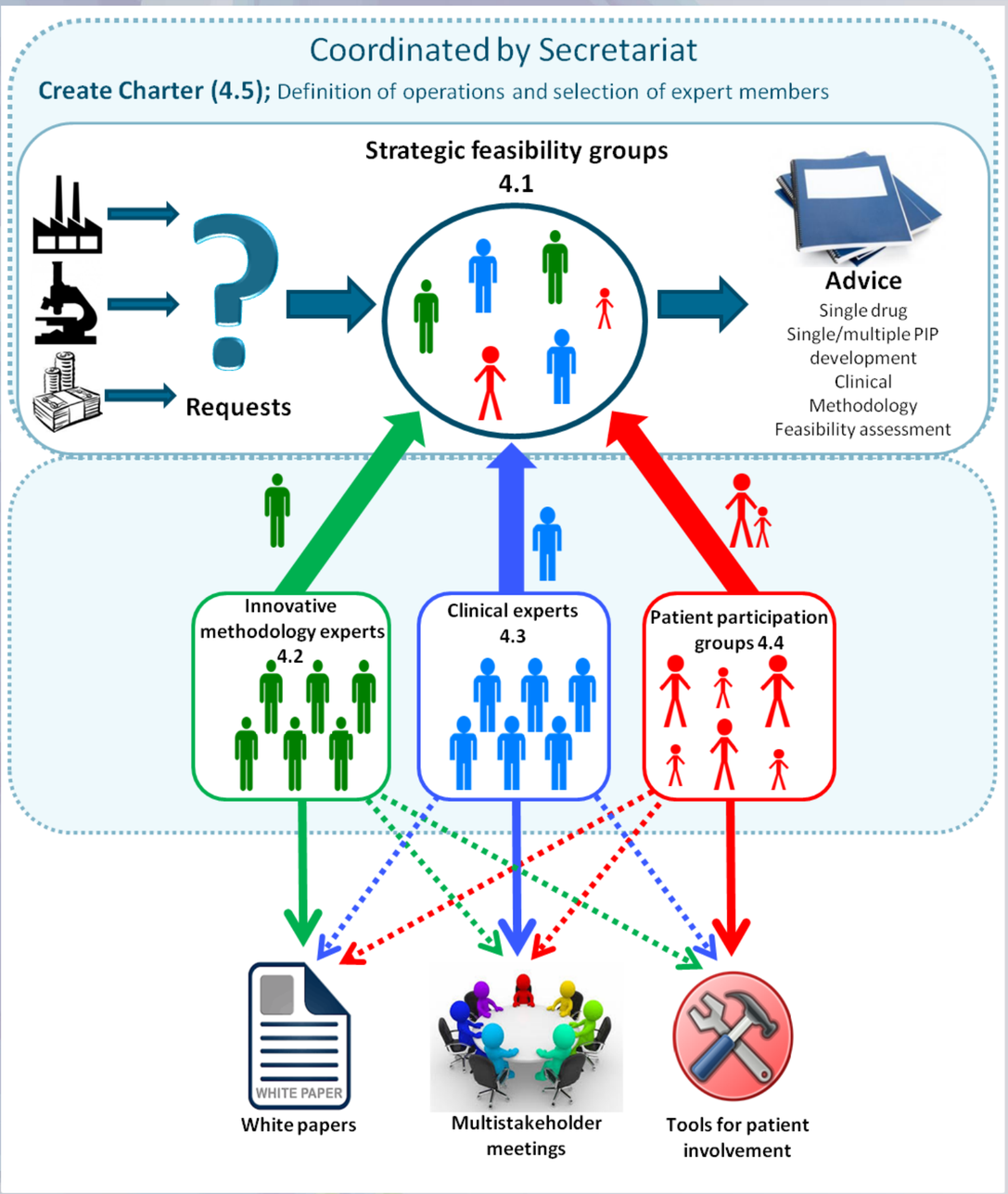
WP4 STRATEGIC FEASIBILITY ADVICE



31 scoping interviews
(7 industry partners & 3 academic sponsors)

6 did not proceed

23 completed

2 ongoing

11 include PPI

21 include one or more Clinical Expert Groups

14 include one or more Innovative Methodology Groups

 # advices per group:

- Adolescent medicine (3)
- Cardiology (3)
- Developmental Pharmacology (1)
- Ethics (5)
- Formulations (3)
- HTA (1)
- Infectious diseases & Vaccinology (3)
- Intensive Care (2)
- Neonatology (3)
- Nephrology (3)
- Neuroscience & Epilepsy (4)
- Oncology/Heamatology (3)
- Omics (2)
- Pharmacovigilance (1)
- Psychiatry (2)
- Respiratory (6)
- RSV (1)
- Study design and Clinical trial methodology (6)
- Other; dermatology (1)

WP6: C4C TRAININGS – C4C ACADEMY

Training subject	When	What
Concept of Paediatric Investigation Plan (PIP)	Registration open (no closing date)!	This short course will provide participants with knowledge on the concepts of a Paediatric Investigation Plan

Courses coming up in Q1 2022:

Training subject
Innovative trial design
Practical tips for setting up gene therapy trials
Carrying out remote clinical trials in paediatrics
Registries and linking with observational studies
Basic principles of Data Visualisation and Business Intelligence

Added value

Core Study Services

- **Core 01** Accelarete study start-up to completion
- **Core 02** Support set-up and conduct of clinical trials
- **Core 03** Create pool of experienced researchers
- **Core 04** Establishing an established network

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Added value

Other services

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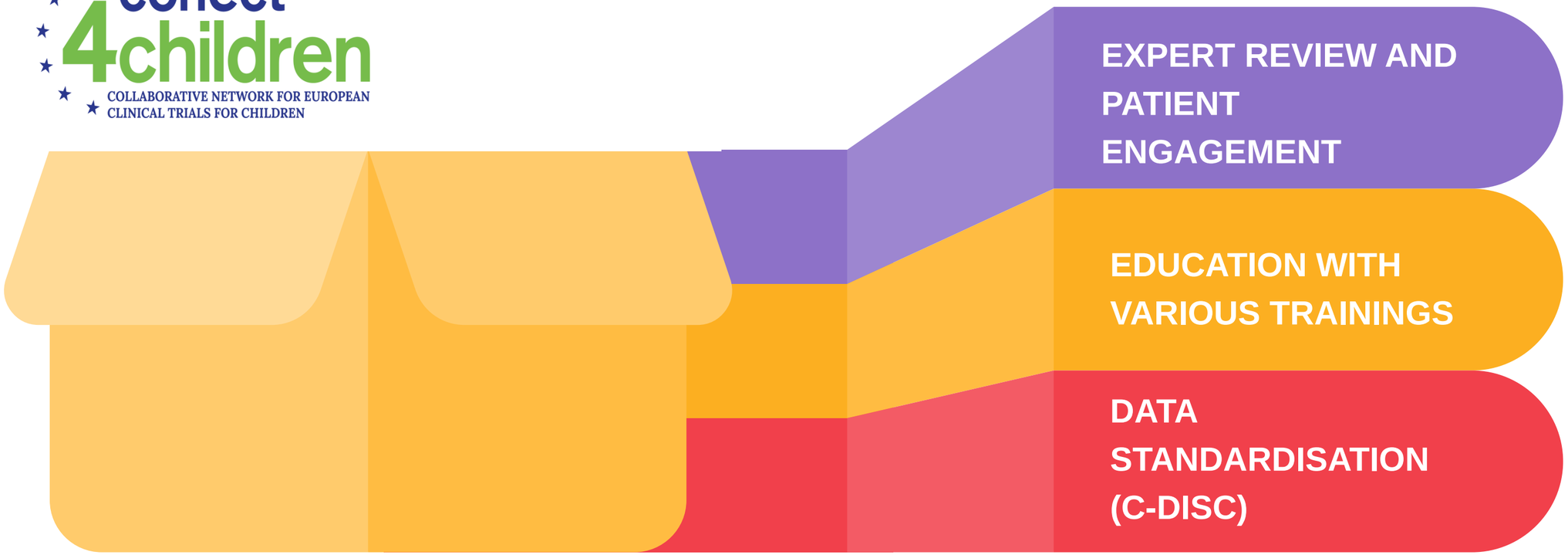

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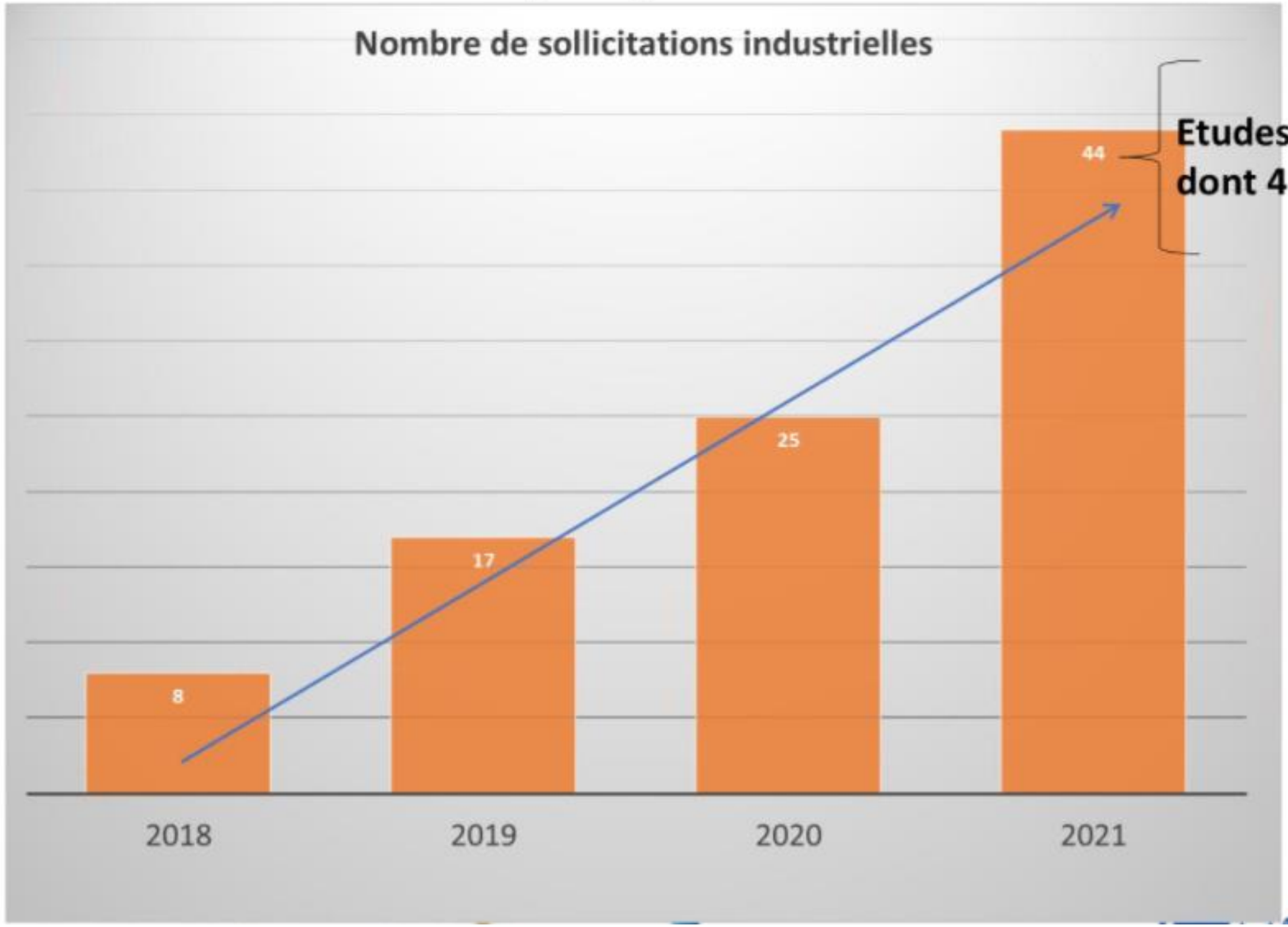
PRELIMINARY RESULTS OF THE C4C ACTIVITIES

1. **Proof of Viability studies (POV)**
   - **Fast** EU-wide CDA completion (cascading CDA system)
   - **Reliable** and **high quality** national reports (Early outreach and Feasibility questionnaire)
   - **Faster** start-up timelines (CDA's, contract support, communication)

2. High-quality group of **Expert advisors** providing over 50 reports to government, sponsors and other stakeholders, aiming to increase and optimize protocols and processes.

3. Sites in Belgium have been actively involved in the **Training courses**, but there is still room for improvement and have more people join them!

Evolution des projets industriels



Courtesy R Hancard feb 2022 French CRN PEDSTART

N3 = NETWORK NATIONAL NETWORKS

Austria	OKIDS
Belgium	BPCRN
Czech Republic	CZECHPHARMNET
Denmark	DANPEDMED
Estonia	UTARTU
Finland	FINPEDMED
France	PEDSTART
Germany	GERMANNETPAET
Greece	HELPNET
Hungary	MCRN
Ireland	IN4KIDS
Italy	INCIPIT
Netherlands	PEDMED-NL
Norway	NORPEDMED
Poland	POLPEDNET
Portugal	STAND4KIDS
Spain	RECLIP
Sweden	SWEDPEDMED
Switzerland	SWISSPEDNET
United Kingdom	NIHR-CRN

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BPCRN learnings

10 to 50 FQ per year

Each FQ takes at average **60 minutes**

Redundant questions **43%** of a FQ

Less than 15% results in a completed study

1. The relatively recent increase in pediatric trials have **substantially burdened sites within Belgium**, with no fee for completing FQ's.
2. **Quality control** by a National central organization could be beneficial to increase feasibility quality and efficiency.
3. A National Organization could facilitate in site selection by having a more personal and **experienced connection with the respective sites**.

SPoC = Single Point of Contact

BPCRN ACTION PLAN : P

- **Prepare readiness**
  - List of centres
    - Where the study can be runned
    - Estimate of the number of patients, and to correct center delivered estimates
  - That the CTU4's are GCP trained
  - Portfolio of performance
- **To prepare prefeasibilities and feasibilities**
  - Part 1 : CTU –logistic portfolio
  - part 2 : general questions
  - Part 3 = disease specific inforamtion= pepare for PI
- **To help with the administration and submission**

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I-ACT FOR CHILDREN (US) – +TRANSATLANTIC COLLABORATION

Institute for Advanced Clinical Trials for Children (US based)

- Contracted by Sponsors or CRO's who sometimes want to achieve **Global clinical trial coverage**
- I-ACT contacts BPCRN to support with **European coverage** (incl Belgian network): support with early country outreach and feasibility completion (European coordination).
- **Q2 2022:** 2x potential new study country outreach (heart failure and migraine)

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SPONSOR AND CRO EARLY COUNTRY OUTREACH/FEASIBILITY

- Prescreened by BPCRN Project Manager
- Only shared with the site teams (site sub-department SPoC and CRC) with dedicated department for the indication
- Prefilled as much as possible
- Reality check / quality control where possible

BPCRN and c4c continuity after April 2024

What comes next?

c4c →New legal Entity (NLE) end 2023

- 2 EU study requests/month (current estimation)

BPCRN → Solidify the national pediatric clinical research network

BPCRN goals:

- Complete an **expert-network within BE** that is sub-discipline specific
- Provide **services against payment**

  Service portfolio:
  - Coordinate Early outreach
  - Coordinate Feasibility questionnaires
  - Facilitate Site start-up
  - Facilitate Study conduct

What does BPCRN need?

- Sponsors/CRO's to request services from BPCRN → **help needed from YOU**

SPoC = Single Point of Contact

BPCRN and c4c continuity after 2024

What is in for you?

- → **Increased number** of study requests /Increase **site visibility**
- → **SPoC** for sponsor (less burden for you)
- → Requests are **prescreened** by BPCRN Project Manager
  Only shared with you **in case you have capability** within this indication
- → Defined **communication flow** is crucial + Readily available and **up-to-date contact list** is imperative! (see next slides)
- → **Prefilled** by BPCRN as much as possible (work in progress!)
- → **Quality control** (pre-)feasibility data → increase country and site selection!
- → **Support / facilitate** start-up & conduct and communication
- → **Training /education** through c4c/NLE → increase expertise

SPoC = Single Point of Contact

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FUTURE PERSPECTIVE OF C4C AND THE BELGIAN NATIONAL NETWORK

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FUTURE CHALLENGES

1. BPCRN as sustainable model
    1. University pediatric centers
    2. Large general hospitals
2. National expert panels (cfr WP4 C4C)
3. COVER
    1. Pediatric CT's in pediatrics
    2. Pediatric CT's in dermatology, psychiatry, etc..
    3. Vaccination's
    4. Rare diseases

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FUTURE CHALLENGES : RARE DISEASES

1. Rare disease = rare patients = rare centers
2. Priority = to get the trial for the often life saving drug in Belgium in at least one centre.
3. To develop a national endorsed strategy for
    1. Initial referral to PI centre cross match with ERN's
    2. Open satellite centres, after the initiation, for the follow up (in contrast with US model of decentralized studies)
4. To cross-match with adult CT network for rare diseases (to be developed)

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BELGIUM NATIONAL NETWORK – CORE TEAM

– From left to right:
Laura Persijn, Sevasti Karamaria, Ann Raes, Daphné Christiaens, Lieve Nuytinck, Eva Degraeuwe and Johan Vande Walle

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