INFORMATION

about the incoming

c4c ADVANCED COURSE

on

PAEDIATRIC CLINICAL TRIALS and PAEDIATRIC DRUG DEVELOPMENT

October 2021 - June 2022

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.

1. Background

The c4c **Advanced Course on paediatric clinical trials and paediatric drug development** (AC) is a postgraduate course provided by the European c4c (conect4children) project, funded by IMI2. The AC is delivered online, in its entirety, via the c4c Academy Platform.

The aim of the AC is to educate health care professionals involved in clinical trials about the scientific, methodological and practical issues involved in the design, conduct, analysis, management and reporting of clinical trials, conducted in the paediatric population. This course will support students to actively participate in CT teams and conduct robust clinical trials in all paediatric age ranges, delivering high quality data. The AC will also support continued professional development by helping learners to acquire additional competences in all the specific aspects of paediatric pharmacology, drug development and evaluation, as well as the regulatory requirements for the use of medicines in the paediatric population.

The course is organized by c4c for nationally selected students belonging to c4c Beneficiaries/Third Parties. It is free of charge.

The course will start on October 18th, 2021, and end on June 16th 2022 (see point 4. Calendar activities for further details).

The AC is awaiting accreditation by Continued Professional Development (CPD) Certification Service .

The information you will find here, has also been given to the National Hubs (NHs) and to EPFIA Partners of the c4c consortium who will select their students.

2. To whom the course is addressed – (Eligibility Criteria to be considered by NHs and EFPIA Partners Referent Persons for Training and Education)

This course is addressed to healthcare professionals involved in clinical trials regarding neonates, children and adolescents. Potential students of this course include Investigators, Sub-investigators, Clinical Research Nurses, Study Coordinators, Data Managers, Clinical Monitors, Scientific Manager working in the National Hubs and linked clinical sites, and any other role involved in paediatric clinical trials.

Students should have a degree in one of the following disciplines:

- Medicine
- Biology and Biotechnology
- Pharmacy
- Chemistry
- Nursing

It is recommended to have a high level of proficiency in English.

3. Contact Details

Course Coordinators:
Responsible overall for the academic content and teaching for the course.

Francesca Rocchi francesca.rocchi@opbg.net
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Course administrative secretariat:
Responsible for enrolment and registration, administrative queries, final certification:

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Virtual Learning Environment (VLE) c4c Academy Platform:
The VLE is a virtual space to support learning, including course materials, discussion forums, and course information. The VLE will also be used to submit work to be assessed.
You can have access to the c4c Academy Platform using this link:
https://www.academyc4c.com/

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4. Enrolment

The maximum number of students who can enrol in this course will be 50. This will include 2 places reserved for each NH and their related clinical sites (40 participants max) and 1 place for each EFPIA Company involved in the c4c Consortium (10 participants max).
The selection of the students will be managed by the NHs (on a country basis) and by EPFIA Partners.
The criteria for selecting the participants should be based on the following:

- The candidates should have the pre-requisite specified in the paragraph n.2 “To whom the course is addressed”
- The candidates should be highly motivated and be able to attend the course in term of time requirement (Motivation letter to be sent by the candidates)
- Specific criteria based on the role in clinical trials, previous expertise, representativeness of different institutions will be evaluated by NHs/EFPIA partners

The enrolment steps will be as follows:

- The enrolment time frame lasts 4 weeks (from Sep 01 to Sept 30);
- Each National Hub can select 2 candidates (who meet the eligibility criteria) and each EFPIA company can select 1 candidate;
- An enrolment password, to access the AC via the c4c VLE Academy Platform, will be given to the selected candidates
- The selected candidates must enrol to the AC within the specified enrolment deadline;
- Once the enrolment deadline expires – ONLY if there are less than 50 students enrolled in the course) – the c4c Academy Management Secretariat will inform the National Hub's Referent Persons for Training and Education that there are still "xx" places available for enrollment
- At this point there will be an "extraordinary enrolment phase" - which will last from Oct 01 to Oct 15 – during which the National Hubs can enrol participants until the max. total number of enrolments (50) is reached. The vacant places will be assigned based on a precedence criteria.
- Once the max. number of people that can be enrolled has been reached, it will be no longer possible to join the AC.
- A waiting listing will be operated in case of early drop-outs/non starters.

5. Course structure and requirements

The **AC** consists of **8 modules**, to be taken in a sequential manner, each module has the duration of 3 weeks except one (module 4), which has a double length. The total duration of the AC will be **29 weeks**, offered entirely online through the c4c Academy VLE Platform. The didactic methodology includes frontal lessons and interactive tools such as asynchronous forums and live webinars for all of the modules.

Each of the 8 modules requires 3 weeks of participation*:

- Week 1 and 2 focus on reading material and lessons
- Week 2 hosts an asynchronous interactive case forum
- Week 3 hosts a webinar

**except module number 4, which has 2 parts of 3 weeks each*

At the end of the first 4 modules, and again at the end of the following 4 modules, there will be an "Interactive team week" hosting interactive team activities related to the four modules, which have been concluded (see point 6, Calendar Activities).

<u>Lessons</u>

The total number of frontal lessons across the whole AC is 76 (6 to 15 lessons for each module).

Each lesson is characterized by a power point presentation along with a voice recording of the teacher presenting the contents. You will have the possibility to download the pdf version of the slides.
As a minimum, each student must complete 80% of the total number of lessons (60) and at least 50% of each module. If students do not meet this criteria, they will be unable to access the final exam.

Forum

During week 2 there will be an asynchronous forum discussion around a specific case. A tutor will guide the discussion, additional material will be provided, if required.
The students are expected to actively participate during this activity, asking questions, providing possible answers and commenting.
In addition to the case forum discussion in week 2, another asynchronous general discussion forum is active for students to ask questions to the teachers and/or to interact each-other during the 3 weeks of each module.

Webinar

The live webinars will act as a forum to discuss all of the critical points and the difficulties encountered during the lessons, as well asany issues raised by the students during the case and discussion forums. Tutors and Teachers will guide the discussion and endeavour to clarify any of their doubts or concerns on the topics, as much as possible. The webinars will be held live at the end of each module, with teachers, tutors and students participating remotely.

On the first day of the AC there will be a special Welcome Webinar as well as, at the end of the AC, there will be a special Closing Webinar.

Interactive team weeks

At the beginning of the AC, the students are organized in four multi-professional teams, according to their educational background, each with a guiding tutor. Since the total number of students participating to the course will be around 50, each team will be made of about 12 students. The teams will get a topic of assignment and they can start to work on this topic together from October 2021 until the first “interactive team week” (in February 2022), when these activities will be concluded. A second round of teamwork will then start and go on until the second “interactive team week” (in June 2022).

The team activities will be planned and organized by a guiding tutor; the assignments contain crosscutting items from different modules. On the last day of both of the “interactive team weeks”, there will be an assignment webinar.

Table. Overall estimated engagement time for the student

Module	**Hours per module**	**Hours per the whole AC** 8 modules (one double length)
Lessons	3	27
Reading material	1	9
Forum	2	18
Webinar	2	18
Sub total	**8**	**72**
Interactive team week	**Hours per interactive team week**	**Hours of interactive team activities for the whole course**
Interactive activities	10	20 hours
Overall Total		**92 hours**

6. Calendar activities

Dates	**Module**	**Webinar (CEST)**
Welcome		Oct 18 at 2.00 – 4.00 pm
18 Oct - 5 Nov	1	Nov 4 at 2.00 – 4.00 pm
8 Nov - 26 Nov	2	Nov 25 at 2.00 – 4.00 pm
29 Nov - 17 Dic	3	Dec 16 at 2.00 – 4.00 pm
17 Dec - 9 Jan		Christmas holidays
10 Jan - 28 Jan	4 (part 1)	Jan 27 at 2.00 – 4.00 pm
31 Jan - 18 Feb	4 (part 2)	Feb 17 at 2.00 – 4.00 pm
21 Feb - 25 Feb	1,2,3,4*	Feb 24 at 2.00 – 4.00 pm
28 Feb - 18 Mar	5	Mar 17 at 2.00 – 4.00 pm
21 Mar - 8 Apr	6	Apr 7 at 2.00 – 4.00 pm
11 Apr - 24 Apr		Easter holidays
25 Apr – 13 May	7	May 12 at 2.00 – 4.00 pm
16 May - 3 June	8	June 2 at 2.00 – 4.00 pm
6 June – 10 June	5,6,7,8*	June 9 at 2.00 – 4.00 pm
13 June -16 June	Final exam	20 -30 min per student
Closure		June 16 at 2.00 – 4.00 pm

*Interactive team week

7. Modules and Teachers

In this section, you will find the list of the modules (with their learning objectives), the teachers and the lessons for each module.

Module 1. Introduction to paediatric drug development

Module Leader: Adriana Ceci (FGB)

Learning objectives

At the end of this module the student should be able to:

- reach full understanding of the rationale of paediatric drug development;
- give introductory knowledge of paediatric clinical trials;
- set paediatric clinical trials within a full paediatric drug development plan.

Lessons

1. Introduction to paediatric drug development – why paediatric drug development is needed, by L. Ruggieri (FGB)
2. Paediatric drug development initiatives at a global level, by D.Bonifazi (FGB)
3. Preclinical and translational research, by A. Ceci (FGB)
4. Clinical trials phases and type definition, by P. Baiardi (FGB)
5. Fundamentals of paediatric clinical trials, V. Giannuzzi (FGB)
6. Alternative methods to generate evidence in paediatrics: benefits and limitations, by O. Della Pasqua (UCL)

Module 2. Developmental Pharmacology

Module Leader: E. Jacqz-Aigrain (INSERM)

Learning objectives

At the end of this module the student should be able to:

- describe the issues of drug evaluation in children associated with growth and maturation and their impact of age on drug disposition;
- understand the innovative pharmacokinetic and pharmacodynamic methods for

drug evaluation in children;

- understand the major impact of pharmacogenomics on the variation in outcome of therapy recommend the importance of genomic markers to explore variability;
- understand how why safety information should be included in drug evaluation in children and adults

Lessons

1. Introduction; children of the world, update in paediatrics, by E. Namburg (KI) and E. Jacqz-Aigrain (INSERM)
2. Molecular pharmacology, by E. Jacqz-Aigrain (INSERM) and J .Kallio (HUS)
3. ADME and impact of growth and maturation, by K.Allegaert (UZLEUVEN) and J. van Den Anker (CNMC)
4. Principles of Physiologically Based Pharmacokinetic Modeling, by C. Knibbe (Leiden University) and G. Kearns (Univ. Arkansas, USA)
5. Principles of population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic modeling, by E. Jacqz-Aigrain (INSERM) and S.Leroux (APHP)
6. Introduction to Pharmacogenetics, by A. Rane (KI) and E. Jacqz-Aigrain (INSERM)
7. Promises of the OMIC sciences, by M. Schwab (IKP)
8. Therapeutic Drug Monitoring: how to evaluate the effect of medication, by S. de Wildt (RUM-MC) and J .Kallio (HUS)
9. Introduction to Pharmacovigilance and risk management, by B. Aurich (APHP) and S. Ito (SickKids, Canada)
10. Introduction to paediatric safety profiling and risk management, by B. Aurich (APHP) and S. Ito (SickKids, Canada)
11. Principles and applications of personalized therapy in children, by M. Schwab (IKP) and E. Jacqz-Aigrain (INSERM)
12. Drugs in pregnancy and during lactation, by K.Allegaert (UZLEUVEN), S. Ito (SickKids, Canada), P. Pokorna (CUNI) and S. de Wildt (RUM-MC),
13. Specific trial issues in neonates, by K.Allegaert (UZLEUVEN) and A. Smiths (UZLEUVEN)
14. Preclinical and translational developmental pharmacology, by G. Kearns (Univ. Arkansas, USA) and E. Jacqz-Aigrain (INSERM)
    Conclusion, by E. Jacqz-Aigrain (INSERM)

Module 3. Regulatory and Ethical Issues Regarding Paediatric Medicines Research and Development

Module Leader: Kristina an Haack (SANOFI)

Learning objectives

At the end of this module the student should be able to:

- understand the principles of ethics in clinical research, with an emphasis on paediatrics;
- understand the regulatory framework and the requirements that are driving pediatric development and registration, including notions of rare diseases, orphan medicines and medicines in pregnancy.

Lessons

1. Introduction and Ethic principles in paediatric clinical research, by Aude Le-Roux (SANOFI)
2. Clinical Trials (Legislation, Approval process, Application, EU database, Safety reporting), by Kristina an Haack (SANOFI)
3. Scientific Advice and HTA (Health Technology Assessment), by Jaana Kallio (HUS)
4. Paediatric Regulation and PIP (Paediatric Investigation Plan), by Gloria Garcia-Palacios (SANOFI)
5. EMA International Paediatric interactions, by Jaana Kallio (HUS)
6. Marketing Authorization, Drug lifecycle, by Gloria Garcia-Palacios (SANOFI)
7. Orphan Medicines and Rare diseases, by Edit Muhari-Stark (MCRN)
   Medicines in pregnancy: Data and issues, by Sylvie Fontecave (SANOFI)

Module 4. Paediatric Clinical Trials: from design to implementation

Module Leaders: Mark Turner (ULIV) and Stephanie Reiter (SERVIER), Donato Bonifazi (CVBF)

Learning objectives

At the end of this module the student should be able to:

- have an integrated knowledge base and basis for action about pediatric clinical trials, that is shared by the whole study team.

Lessons

1. Introduction: Clinical Trial Development & Management, by Mark Turner (ULIV), Donato Bonifazi (CVBF) and Oana B. Poenaru (SERVIER)
2. Clinical study protocol and specificities of paediatric trial, by Mark Turner (ULIV), Oana B. Poenaru (SERVIER) and Mariagrazia Felisi (CVBF)
3. Site feasibility, selection & qualification, by Ana Dilo (CVBF), Sergey Grankov (SERVIER) and Alessandro Zuddas (UNICA)
4. Clinical project management, by Mark Turner (ULIV) and Sergey Grankov (SERVIER)
5. Monitoring plan, Risk based monitoring, by Loic Notelet (SANOFI)
6. Data management, by Sophie Brun (SERVIER) and Mariagrazia Felisi (CVBF)
7. Preparing for site initiation and activation, by Stephanie Reiter (SERVIER), Ana Dilo (CVBF) and Alessandro Zuddas (UNICA)
8. Key documents readiness, by Mariagrazia Felisi (CVBF), Stephanie Reiter (SERVIER) and Arlinda Demeti (CVBF)
9. Trial conduct: operational and strategic decisions, by Mark Turner (ULIV), Donato Bonifazi (CVBF) and Sergey Grankov (SERVIER)
10. Trial conduct: quality aspects, by Loic Notelet (SANOFI)
11. Trial conduct: data management & monitoring, by Sophie Brun (SERVIER) and Silvia Pulici (CVBF)
12. Trial conduct: logistics, by Mark Turner (ULIV) and Mandy Wan (Guy's and St. Thomas' NHS Foundation Trust)
13. Preparing for study and site closure, by Stephanie Reiter (SERVIER) and Silvia Pulici (CVBF)
14. Sharing data after end of clinical trials: Clinical study report & publications, by Mark Turner (ULIV), Oana B. Poenaru (SERVIER) and Alessandro Zuddas (UNICA)

Module 5. Investigational Medicinal Product (IMP) management in Clinical Trials and Paediatric Drug Formulations

Module Leader: Catherine Tuleu (UCL)

Learning objectives

At the end of this module the student should be able to:

- identify the requirements and issues related to formulation of age-adapted dosage forms
- understand the procedures to ensure the quality of paediatric medicines.

Lessons

1. Pharmaceutical Safety: Paediatric Medication Errors, by M. Ghaleb (University of Hertfordshire)
2. Challenges of Administering Medicines to Neonates, by S. Arenas-Lopez (GSTT-NHS)
3. Quality of Paediatric Medicines: The European Medicines Agency Paediatric Investigational Plan (Part 1 and 2), by Piotr Kozarewicz (EMA)
4. Paediatric Drug Delivery and Drug Administration in children (Part 1 and 2), by C. Tuleu (UCL)
5. Pharmaceutical Safety: excipients, by S. Salunke (UCL)
6. In-vitro biopharmaceutical methods in the development of oral dosage forms for children, by H. Batchelor (University of Strathclyde)
7. GMP-GCP in CTs: Investigational Medicinal Product management (Part 1 and 2), by M. Wan (GSTT-NHS)

Module 6. Pharmacovigilance

Module Leader: Alpha Diallo (INSERM)

Learning objectives

At the end of this module the student should be able to:

- have an integrated knowledge basis regarding the pharmacovigilance system in pediatric clinical trial and the specificities of risks due to drug administration in the pediatric population.

Lessons

1. Guideline and legislation in Pharmacovigilance regarding pediatric medicines research: EU and FDA approaches and perspectives, by E. Bigagli (University of Florence)
2. Susceptibility to develop adverse reactions: difference between adult and paediatric populations, by M. Figarella (INSERM)
3. Safety monitoring and reporting in children, by L. Levoyer (INSERM)
4. Assessment of adverse events (Severity, causality, expectedness), by A. Diallo (INSERM)
5. Developing standardized Standard Operating Procedures and safety matters for paediatric protocols, by M. Figarella (INSERM)
6. Signal detection and pharmaco-epidemiology in paediatric population, by V. Terzic (INSERM)

7. Benefit-risk considerations in children and risk minimisation
    7.1: Risk-Benefit Assessment - Basic principles of risk: Definitions and aspects of methods, by L. Levoyer (INSERM)
    7.2: Risk Management, by L. Levoyer (INSERM)
8. Pharmacovigilance and vaccines in paediatric population, by N. Mercier (INSERM)

Module 7. Patients and Parents Involvement in CTs

Module Leader: Begonia Nafria (FSJD)

Learning objectives

At the end of this module the student should be able to:

- understand the patients' perspectives on paediatric clinical trials;
- identify the different phases of the drug development in which patients and/or caregivers can be involved;
- design an activity of paediatric patients involvement in a clinical trial.

Lessons

1. Introduction to the patients' engagement in drug development: definition of terms (engagement, involvement and participation), by Begonia Nafria (FSJD).
2. Benefits of involving patients, both for the patients and for the projects,by Begonia Nafria (FSJD).
3. Active role of patients along the drug development process: research priorities; research design and planning; research conduct and operations; dissemination, communication and post-approval, by Begonia Nafria (FSJD).
4. Importance of involving patients in early phases: research priorities and protocol design, by Begonia Nafria (FSJD).
5. Methodologies for involving patients in drug development, by Begonia Nafria (FSJD).
6. Involvement of peadiatric patients: how to design activities of patient engagement for children. Diversity. Special needs, by Begonia Nafria (FSJD).
7. Tools to design activities of patient engagement in paediatric clinical trials, by Begonia Nafria (FSJD).
8. c4c model of patients and public involvement, by Nuria Noel (FSJD).
9. Measuring the impact of patient's involvement in clinical trials, by Begonia Nafria (FSJD).

Module 8. Biomarkers and Innovative Tools in Paediatric Clinical Drug Development

Module leader: Oscar Della Pasqua (UCL)

Learning objectives

At the end of this module the student should be able to:

- identify the requirements and opportunities for use of biomarkers in the evaluation of efficacy and safety in paediatric drug development;
- discuss opportunities and challenges for the evaluation of efficacy and safety in children by using innovative tools.

Lessons

1. Biomarkers: definition, requirements and opportunities for their use in paediatric drug development, by O. Della Pasqua (UCL)
2. Biomarkers validation and regulatory qualification (EMA), by F. Musuamba (EMA)
3. Biomarkers and dose rationale in paediatric drug development, by O. Della Pasqua (UCL)
4. Challenges associated to the use of biomarkers in paediatric drug development, by O. Della Pasqua (UCL)
5. Biomarker-based trials designs and personalised medicine, implementation of clinical trials using biomarkers in adults for later extrapolation in children, by O. Della Pasqua (UCL)
6. Statistical approaches: flexible protocol designs, and real world evidence, by Hakim-Moulay Dehbi (UCL)
7. Quantitative Clinical Pharmacology approaches: PK/PD modelling and simulation, by S. D'Agate (UCL)
8. Bayesian approach and benefit/risks assessment of drugs in children, by S. D'Agate (UCL)
9. Extrapolation from adults to children / across disease conditions, by S. Oosterholt (UCL)

8. Final exam and certification

At the end of the AC a certificate by the c4c Educational Board will be released to participants, provided that the student has actively participated in the different parts of the course including the interactive activities in Case forums, general discussion forum and team work. The active participation of the student is tracked on the platform. Students must meet

the minimum criteria to receive the certificate: complete at least 80% of the total lessons and 50% of each Module, and pass the final exam.
The final examination (about 20-30 minutes long) will consist of an online f2f interview, with at least 2 teachers of the AC participating. Its purpose will be to assess if the student has achieved the learning outcomes of the course.

9. Accreditation of the Course

The AC will be submitted for accreditation assessment to the Continued Professional Development (CPD) Certification Service. Courses with CPD accreditation show that the learning activity has reached required Continuing Professional Development standards and benchmarks.