

INFORMATION
about the upcoming
c4c ADVANCED COURSE
on
PAEDIATRIC CLINICAL TRIALS
& PAEDIATRIC DRUG DEVELOPMENT
2nd Edition
September 2023 - April 2024

1. Background

The c4c Advanced Course on Paediatric Clinical Trials & Paediatric Drug Development (AC):

- ✓ **Postgraduate** course
- ✓ From the European **c4c (conect4children)** project, funded by IMI2.
- ✓ Delivered **online**, in its entirety, via the c4c Academy Platform.
- ✓ **Free** of charge
- ✓ **Accredited** by Continued Professional Development (CPD) Certification Service.
- ✓ **Develop** additional competencies in:
 - paediatric pharmacology,
 - drug development and evaluation
 - regulatory requirements for the use of medicines in the paediatric population

COURSE DATES: 11TH SEPTEMBER 2023 – 23RD APRIL 2024

2. Purpose

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 supports students to actively participate in Clinical Trial (CT) teams & conduct robust CTs in all paediatric age ranges, delivering high quality data.

3. Who should apply?

- ✓ **Only available** to students working with **c4c or EFPIA partners**
- ✓ Health Care Professionals involved in Paediatric Clinical Trials
- ✓ High level of **proficiency in English**

Position	Education
Investigators	Medicine
Clinical Research Nurses	Biology & Biotechnology
Study Coordinators	Pharmacy
Data Managers	Chemistry
Clinical Monitors	Nursing



4. Contact Details

Course Coordinators:

Responsible overall for the academic content and teaching for the course.

- Francesca Rocchi francesca.rocchi@opbg.net
- Jussi Mertsola jussi.mertsola@utu.fi
- Gian Luigi Spadoni gianluigi.spadoni@opbg.net
- Alessio Ceccherelli alessio.ceccherelli@uniroma2.it

Course administrative secretariat:

Enrolment and registration, administrative queries, final certification:

- Giulia Neccia enrolment-c4c@opbg.net

c4c Academy Platform is a Virtual Learning Environment to:

- ✓ Provide course materials
- ✓ Hold discussion forums,
- ✓ Supply course information.
- ✓ Submit assignments.

Academy Platform can be accessed using this link:

<https://www.academyc4c.com/>

c4c Academy Platform Contact:

Alessio Ceccherelli & Valerio Ferri c4c@scuolaiad.it



5. Enrolment

- ✓ Maximum number of students - **50**.
 - **2 places** per National Hub (40 participants)
 - **1 place** per EFPIA Company involved in the c4c (10 participants).

- ✓ Selection of the students is managed by the AC coordinators in consultation with the NHs and the EPFIA Partners.
- ✓ Selection Criteria:
 - Meet Criteria in **3. Who Should Apply**
 - Specific criteria based on previous experience in clinical trials,
 - Representativeness of different institutions and countries
 - Confirm that students understand the course structure and time commitment

Enrolment procedure:

Enrolment dates: April 1st – May 15th 2023

1. Submit course application (available [here](#) on the c4c website) **before** midnight May 15th, 2023
2. If less than 50 applicants have enrolled by May 15th, National Hubs and the EFPIA Partners will be informed of places available.
3. From **May 15th – June 15th** the National Hubs and the EFPIA Partners can inform if they have more students that are interested in enrolling.
4. The remaining vacant places will be filled until the maximum of participants is reached.
5. Final selection of students will be announced before **June 30th, 2023**.
6. A waiting listing will be operated in case of early drop-outs/non-starters during the first month of the AC.



6. Course structure and requirements

- Students will be divided into four teams (white, red, blue & green team)
- The AC consists of **8 modules**, to be taken in a sequential manner.
- Each module **lasts 3 weeks** except one (module 4), #

- Week 1: Reading material and lessons;
 - Week 2: Interactive case forum;
 - Week 3: Live webinar, with active participation from students and teachers.
- **Module 4** is made up of 2 parts, each lasting 3 weeks (total of 6 weeks).
- The total duration of the AC is **29 weeks**:
- 27 weeks for the modules + 2 “assignment weeks”
- Each team **completes two assignments** during the course.
- Assignment week 1: End of Module 4
 - Assignment week 2: End of Module 8
 - Teams will present their assignments at this time
- In addition to video-lessons, articles and links, the course includes interactive tools such as **discussion forums** and live **webinars**.
- The teams have guiding tutors and mentors during the AC.



Lessons

- **76 lessons** in total (6 to 15 lessons per module - see section 10)
- Each lesson involves
- a **PowerPoint** presentation
 - **recording** of the teacher presenting the contents
 - option to **download** the PDF-version of the slides.
 - Some of the lessons in module 2 are **for experts only**
(Further explanations about this definition will be given at the beginning of the module).
 - Students must watch **at least 50% of the lessons** of each module
(Note: in Module 2, 50% of basic lessons)
 - Teachers and tutors will recommend “**core lessons**”, based on background and the professional role of each student.



Self-assessment quiz

- **At the beginning of each module**, students will complete a short self-assessment quiz about their present knowledge of the topics in the module.
- The quiz contains multiple choice questions.
- The same quiz is repeated at the **end of the module**.
- This time the student needs to **select answers until all are correct**. The number of selections will be counted as one indicator of learning.
- This is one of the requirements for the student to be eligible to obtain the final AC certificate.



Case Discussion Forum and General Discussion Forum

- Week 2 of each module has a specific case study discussion forum
- The discussion is guided by a tutor
- Additional material may be provided.
- Actively participation is required:
 - asking questions,
 - providing possible answers
 - commenting.

A **general discussion forum** is active for student questions or comments and to interact with tutors and each-other during all the 3 weeks of each module.



Webinars

- Each module has 1 webinar (module 4 has 2) – **9 module webinars**
- The live (real time) two-hours webinars act as a forum to discuss:
 - all the critical points of the module
 - any difficulties encountered during the module,
 - any issues raised by the students during the forums.
- Tutors and teachers will guide the discussion and endeavour to clarify any doubts or concerns on the topics, as much as possible.

There are also **5 other webinars**:

- **Welcome webinar**: First day of the course;
- **Teamwork webinar**: Few weeks after the beginning of the course, to explain teamwork to students and host the first interaction with the students and tutors and mentors;
- **Assignment webinars**: During the 2 assignment weeks, when the teams present the summary of the assignments
- **Closing webinar**: Last day of the course

It is mandatory, for the AC certificate, to attend at least 6 of the 9 “module webinars” live.

All the webinars are recorded and available on the platform until the end of the course.



Teamwork

- Students are organized into **four multi-disciplinary teams** (white, red, blue & green),
- Teams are based on educational background.
- Each team has a guiding **tutor**. The team activities will be planned and organized by a guiding tutor. The assignments contain crosscutting items from different modules.
- Each will also have a **mentor**. (The mentors are students of the previous AC and will help guide assignments)
- Each team will have approximately **12 students**.
- The teams will get **2 assignment topics** and will work together using “teamwork webinar”
- The first presentation will be in **January 2024** (Assignment week #1)
- The second presentation will be in **April 2024** (Assignment week #2)



Overall estimated time for the student

Students must be aware of the time requirement prior to enrolment.

- The lessons can be watched when the students want,
- Interactive activities occur on predetermined days.
- The interactive activities involve a lively participation of the students are:
 - the case forum,
 - the webinars and
 - especially the teamwork, aimed at carrying out an assignment, with the other students of the team, to be presented in a dedicated webinar.

The hours calculated in the table below should be considered **approximate**, due to many variables such as the professional experience of the student.

Table: Overall estimated engagement time for the student

Module activities	Hours per module	Total Hours for AC 8 modules (one double length)
Lessons	3	27
Reading material	1	9
Case Forum	3	27
Webinar	2	18
Sub total	9	81
Teamwork activities	Hours per assignment	Total Hours for AC
Assignment development and presentation	10	20
Special webinars	Hours per webinar	Total Hours for AC
Opening, closing and teamwork webinar	2	6
Overall Total		about 107 hours (3.7 hrs/week)



7. Calendar activities

Dates	Module	Webinar (CET)
Welcome (11 Sep 2023)		Sep 11 2:00 – 4:00 pm
11 Sep - 29 Sep	1	Sep 28 2:00 – 4:00 pm
Teamwork		Oct 5 2:00 – 4:00 pm
2 Oct - 20 Oct	2	Oct 19 2:00 – 4:00 pm
23 Oct - 10 Nov	3	Nov 9 2:00 – 4:00 pm
13 Nov - 1 Dec	4 (part 1)	Nov 30 2:00 - 4:00 pm
4 Dec - 21 Dec	4 (part 2)	Dec 21 2:00 – 4:00 pm
22 Dec - 7 Jan	Christmas Holidays	
8 Jan - 12 Jan	Assignment week (1-4)	Jan 11 2:00 – 4:00 pm
15 Jan - 2 Feb	5	Feb 1 2:00 – 4:00 pm
5 Feb - 23 Feb	6	Feb 22 2:00 – 4:00 pm
26 Feb – 15 Mar	7	Mar 14 2:00 – 4:00 pm
18 Mar – 29 Mar	8 (1st-2nd week)	
30 Mar - 7 Apr	Easter Holidays	
8 Apr – 12 Apr	8 (3rd week)	Apr 11 2.00 – 4.00 pm
15 Apr – 19 Apr	Assignment week (5-8)	April 18 2.00 – 4.00 pm
Closure (23 April 2024)		April 23 2:00 - 4:00 pm

Please note that all webinars occur on a Thursday from 2:00 pm to 4:00 pm (CET), except the opening webinar which occurs on a Monday and the closing webinar which occurs on a Tuesday, at the same time.

8. Certification

At the end of the AC a certificate from the c4c Educational Board will be provided to the participants if the student has:

- ✓ answered the quizzes of all the eight modules.
- ✓ watched at **least 50% of the lessons** of each module (in Module 2 only 50% of the basic lessons)
- ✓ **participated** in the **interactive activities** in case forums and teamwork.
- ✓ actively followed at least **6 of the 9 webinars** and the **teamwork webinar**.
- ✓ actively participated in the **“teamwork webinar”**
- ✓ answered the **evaluation questionnaire** at the end of **each module** and at the end of full course based on the **entire AC**.

The active participation of the student is tracked on the platform.

9. Accreditation of the Course

The AC is accredited by **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.

10. The modules: learning objectives, teachers and lessons.

In this section, you will find the list of the modules, their learning objectives, the names of the teachers who developed the lessons and the titles of the lessons in each module.

Other material, such as articles and/or links will be provided to the students.

As previously mentioned, the students need to carry-out a self-assessment quiz at the beginning and at the end of each module.

The student needs also to complete a short module evaluation questionnaire about the course material and interactions at the end of each module.

At the end of the course there will be also one more summary satisfaction questionnaire.

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 Leaders: E. Jacqz-Aigrain (INSERM) and K. Allegaert (UZLEUVEN)

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 the 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 and the importance of genomic markers to explore variability;
- understand how and why safety information should be included in drug evaluation in children and adults

The lessons of this module have different learning outcome levels. On this basis they have been classified as “*basic*” or “*for experts*”. Further explanations about this differentiation will be given at the beginning of the module.

Lessons

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

12. Drugs in pregnancy and during lactation, by K. Allegaert (UZLEUVEN), S. Ito (SickKids, Canada), P. Pokorna (CUNI) and S. de Wildt (RUM-MC), *for experts (neonatologists)*
13. Specific trial issues in neonates, by K. Allegaert (UZLEUVEN) and A. Smiths (UZLEUVEN), *for experts (neonatologists)*
14. Preclinical and translational developmental pharmacology, by G. Kearns (Univ. Arkansas, USA) and E. Jacqz-Aigrain (INSERM), *for experts*
15. Conclusion/Key messages, by E. Jacqz-Aigrain (INSERM), *basic and for experts*

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)
8. 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 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 paediatric 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)