EAHP Position Paper on Clinical Trials

Meeting future healthcare challenges!

Clinical trials are essential for continuously improving patient outcomes and their quality of life. Medicines used in clinical trials need to be securely managed by trained personnel capable to pertain their storage, dispensing, return and destruction. Hospital pharmacists are members of the multidisciplinary team needed for safely managing clinical trials. Within the European Union, clinical trials are governed by the Clinical Trials Regulation which harmonises the processes for assessment and supervision.[1] This piece of legislation that entered into application in January 2022, also made the process for multinational trials more efficient due to the single online platform known as the Clinical Trials Information System (CTIS).[2]

The European Association of Hospital Pharmacists (EAHP) outlines in this position paper the role of the hospital pharmacists in clinical trials, provides information on the need to involve different patient groups, reflects on the improvements in Europe's clinical trial landscape and discusses the role of ethics committees in clinical trials.

EAHP calls on national governments to recognise the important roles that hospital pharmacists play in clinical trials by requiring their involvement to increase patient safety.

EAHP encourages regulators to further improve training on clinical trials by anchoring it into both undergraduate and continuing education of pharmacists.

EAHP recognises that not all patient groups are suitable candidates or fully represented in clinical trials. Where appropriate, efforts should be made – taking into account also all relevant constraints – to create clinical trials that also study the effects of new treatment options in diverse patient populations, so that also these groups could be provided with access to new medicines once approved.

EAHP underlines the importance of utilising the full potential of the EU Clinical Trial Regulation by swiftly putting all necessary measures in place at the national level to successfully transition to this new regime.

EAHP urges the Member States to ensure that the role of ethics committees under the new Clinical Trial Regulation remains strong in the interest of clinical trial participants.

The role of the hospital pharmacist in clinical trials

Clinical trials are complex and require the involvement of different healthcare professionals.[3] Multidisciplinary cooperation is essential for their success. The care team should involve principal and sub-investigators, clinical research coordinators, pharmacists and other healthcare professionals involved in clinical trials.[4] One of the key contributions of the pharmacist is the promotion of patient safety by

[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158/1.

[2] European Medicines Agency, Clinical trials in the European Union, available at: https://euclinicaltrials.eu/home (last visited on 23 February 2022).

[3] Racedo Africano, Carlos J et al. "Perspectives on a Multidisciplinary Team Approach to Implementation of Planned Emergent Use Research." Medical science monitor : international medical journal of experimental and clinical research vol. 21 2794-800. 19 Sep. 2015, doi:10.12659/MSM.894327.

[4] Moreira Lima Gamboa M, Tesainer Brunetto A, Ferreira Dos Santos ME, Gregianin L. The pharmacists' role in clinical research. Farm Hosp. 2011 Nov-Dec;35(6):341-2. doi: 10.1016/j.farma.2010.10.006. Epub 2011 Jun 23. PMID: 21703894.

collaborating in the development of a research protocol, reviewing as a member of an advisory committee, establishing mechanisms that contribute to safety, and assuring compliance with local and national regulations and standards. Another area of engagement for hospital pharmacists in clinical trials is the procurement, compounding, handling and storage of investigational medicinal products that are part of a clinical trial, according to Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) guidelines.[5] This closely interlinks with the direct collaboration of the pharmacist and the rest of the multidisciplinary team on pharmaceutical aspects such as composition, supervision of indications, dosage, contraindications, adverse effects and interactions of investigational medicinal products.

Hospital pharmacists are at the forefront of patient care and consequently also have a significant impact on patient management and thus should be further integrated into the work of ethics committees.[6] Linked to the clinical trial roll-out as a whole, the hospital pharmacist can function as a connector between the promoters, the competent authority and the local scientific officers.[7] Investigational medicinal products have specific risks that need to be managed and medication errors may occur in clinical trials, possibly associated with adverse reactions.[8] The hospital pharmacist due to expertise on pharmaceutical aspects is an important figure that can help with the management of these risks. In accordance with Section 6.5 of the European Statements of Hospital Pharmacy, the hospital pharmacist should be actively involved in clinical trials of medicines.[9] However, despite the advantages of hospital pharmacy involvement in clinical trials, their pharmaceutical expertise is not yet fully utilised across Europe.[10] **EAHP calls on national governments to recognise the important roles that hospital pharmacists play in clinical trials by requiring their involvement to increase patient safety.**

Particular attention must be paid to all medication processes within clinical trials related to high-risk and hazardous medicines, medicines with unknown toxicity/occupational safety profiles and those of a particular nature, such as radiopharmaceuticals and advanced therapy medicinal products (ATMPs), including gene therapy medicinal products. Specific rules, precautions and practical specificities that apply for some of these medicinal products, such as exemptions from authorisation and GMP requirements for diagnostic radiopharmaceuticals, specific rules for labelling or environmental safeguards for genetically modified ATMPs need to be further considered in the training of hospital pharmacists and other professionals involved in clinical trials .[11]

To best carry out its functions as a member of the multidisciplinary clinical trial team, the pharmacist must be competent with the GCP guidelines, research protocol, informed consent form, investigator's brochure, and standard operating procedures of the research centre which include regulatory, ethical, and legal requirements.[12] To ensure that the aims of the Clinical Trial Regulation, including the promotion of higher standards in patient's safety and increasing transparency in clinical trials, are met, education and training specifically targeted to clinical trials is essential for ensuring that each member of the team, including the

[5] Brown JN, Britnell SR, Stivers AP, Cruz JL. Medication Safety in Clinical Trials: Role of the Pharmacist in Optimizing Practice, Collaboration, and Education to Reduce Errors. Yale J Biol Med. 2017;90(1):125-133. Published 2017 Mar 29.

[6] Moreira Lima Gamboa M, Tesainer Brunetto A, Ferreira Dos Santos ME, Gregianin L. The pharmacists' role in clinical research. Farm Hosp. 2011 Nov-Dec;35(6):341-2. doi: 10.1016/j.farma.2010.10.006. Epub 2011 Jun 23. PMID: 21703894.

[7] Bragazzi NL, Mansour M, Bonsignore A, Ciliberti R. The Role of Hospital and Community Pharmacists in the Management of COVID-19: Towards an Expanded Definition of the Roles, Responsibilities, and Duties of the Pharmacist. Pharmacy 2020, 8, 140. https://doi.org/10.3390/pharmacy8030140.

[8] Delavoipière E, Fourage C, Macro M, Olivier-Abbal P, Fleck C, Mouchel C, Gavard M, Petitpain N, Muller C, Franceschi MP, Savary C, Fournel F, Chaillot F, Alix A, Peyro-Saint-Paul L; REVISE. Déclaration des erreurs médicamenteuses dans les recherches portant sur le médicament : place du pharmacien des essais cliniques ? [Medication errors reporting in drug clinical trials: Role of the clinical research pharmacist?]. Therapie. 2021 Nov-Dec;76(6):735-742. French. doi: 10.1016/j.therap.2021.02.002. Epub 2021 Feb 5. PMID: 33676756.

[9] The European Statements of Hospital Pharmacy, European Journal of Hospital Pharmacy 2014;21:256-258

[10] Bogdanova L, et al. Ad hoc study of the role of hospital pharmacists in clinical trials in Bulgaria. Scripta Scientifica Pharmaceutica, [S.l.], v. 1, n. 1, p. 20-24, jun. 2014. ISSN 2367-5500.

[11] Bormans G, Buck A, Chiti A, et al. Position statement on radiopharmaceutical production for clinical trials. *EJNMMI radiopharm. chem.* 2, 12 (2017). https://doi.org/10.1186/s41181-017-0031-y. Tenti G, Simonetti MT, Bochicchio G, Martinelli, Main changes in European Clinical Trials Regulation (No 536/2014), Contemporary Clinical Trials Communications, Volume 11, 2018, 99-101,ISSN 2451-8654, https://doi.org/10.1016/j.conctc.2018.05.014.

[12] Moreira Lima Gamboa M, Tesainer Brunetto A, Ferreira Dos Santos ME, Gregianin L. The pharmacists' role in clinical research. Farm Hosp. 2011 Nov-Dec;35(6):341-2. doi: 10.1016/j.farma.2010.10.006. Epub 2011 Jun 23. PMID: 21703894.

pharmacist, can optimally contribute to the success of a clinical trial.[13] This training should also focus on the preparation/compounding of high-risk and hazardous medicines, medicines with unknown toxicity/occupational safety profiles and those of a particular nature, such as radiopharmaceuticals and ATMPs. **EAHP encourages regulators to further improve training on clinical trials by anchoring it into both undergraduate and continuing education of pharmacists.**

Clinical trials for special populations

Special populations such as children, the elderly and women (non-pregnant and pregnant) are underrepresented in clinical trials due to the need for additional consideration with regard to clinical research.[14] To protect these vulnerable groups specific regulations need to be adhered to when performing clinical trials with special populations. Although the number of paediatric clinical trials increased considerably between 2007 and 2015 the gap between the amount of adult and paediatric trials is still wide.[15] For paediatric patients research is for example affected by ethical concerns, recruitment challenges, the lack of clear criteria for evaluating the potential risks of their exposure in a trial, the lack of availability of child-appropriate dosages and application forms and the costs of paediatric clinical trials.[16] Paediatric investigation plans (PIPs) need to be strongly encouraged.

While older patients are proportionately major users of medicine, this group is underrepresented or even excluded from many clinical trials that generate the evidence base for healthcare interventions. Yet it is recognised at the international level that due to potential differences in pharmacokinetics, pharmacodynamics, disease-drug interactions, drug-drug interactions, and clinical response that can occur in the geriatric population, conclusions reached in studies of adults cannot be extrapolated to the treatment of older patient populations.[17] EU Clinical Trial Register data from 2019 indicate that, out of a total of 19,447 ongoing clinical trials, 14,026 have been designed for adults and the older persons (72%). However, a caveat is that the database does not adequately display trials involving only older individuals. This patient group is usually included in the broader term "adults".[18] Therefore, the results of the Clinical Trial Register offer a distorted image of the clinical trials landscape for this patient group. Owed to the lack of clinical trial data for the older population, treatment decisions are in daily practice routinely based on medical data derived from studies of younger adults. In these situations, practitioners are left to treat patients over the age of 65 without adequate knowledge of older adults' response to medication, dosing ranges in acute and long-term use, side effect profiles, potential for accumulation in the body, and drug-drug interactions.[19]

EAHP recognises that not all patient groups are suitable candidates or fully represented in clinical trials. Where appropriate, efforts should be made – taking into account also all relevant constraints – to create clinical trials that also study the effects of new treatment options in diverse patient populations[20], so that also these groups could be provided with access to new medicines once approved.

[13] Cagnazzo C, Campora S, Ferretti E, Arizio F, Marchesi E. New European Clinical Trial Regulation: perception and expectations in Italy. Ann Oncol. 2017 Jul 1;28(7):1648-1654. doi: 10.1093/annonc/mdx153. PMID: 28368461.

[14] Joseph PD, Craig JC, and Caldwell PHY. (2015) Clinical trials in children, Br J Clin Pharmacol, 79, 357– 369, doi: 10.1111/bcp.12305. Grimsrud, K, Sherwin C, Constance J, Tak C, Zuppa A, Spigarelli M, Mihalopoulos N. (2015). Special population considerations and regulatory affairs for clinical research. Clinical Research and Regulatory Affairs. 32. 10.3109/10601333.2015.1001900.

[15] Study on the economic impact of the Paediatric Regulation, including its rewards and incentives. Technopolis Group, December 2016, available at (last visited on 29 March 2022) https://op.europa.eu/en/publication-detail/-/publication/78a07c95-0703-11e8-b8f5-01aa75ed71a1.

[16] Toma M, Felisi M, Bonifazi D, Bonifazi F, Giannuzzi V, Reggiardo G, de Wildt S, Ceci A and TEDDY European Network of Excellence for Paediatric Research (2021) Paediatric Medicines in Europe: The Paediatric Regulation—Is It Time for Reform? Front. Med. 8:593281. doi: 10.3389/fmed.2021.593281.

[17] ICH. "Guidance for Industry: E7 Studies in Support of Special Populations: Geriatrics. Questions and Answers.," February 2012, ICH.

[18] EU Clinical Trials Register, available at https://www.clinicaltrialsregister.eu/ctrsearch/search?query=&age=elderly&status=ongoing&gender=both.

[19] Alvino S, "Elderly Representation In Clinical Trials: Not A Gray Area", InVentiv Health Clinical, April 2014, available at http://www.clinicalleader.com/doc/elderly-representation-in-clinical-trials-not-a-gray-area-0001 .

[20] The term diverse patient population includes for example pediatric patients, pregnant and breastfeeding women, the elderly, etc.

Further improving the European clinical trial landscape

The new EU Clinical Trial Regulation is based on three fundamental pillars: harmonisation of the procedures for carrying out clinical trials due to the submission of a single e-dossier through a new information system, public disclosure of information obtained from clinical trials to increase trust and reliability and simplified safety reporting requirements.[21] Through the introduction of the single European electronic portal for submitting trials, the EU seeks to accelerate the application process by simplifying and harmonising the administrative requirements for multicentre clinical trials.[22] Also, access to information will improve due to the publication of a non-technical, plain-language summary of clinical trial results.[23] To majorly change Europe's role in the global clinical trial landscape, efforts need to be made throughout the transition period, lasting until January 2025. **Consequently, EAHP underlines the importance of utilising the full potential of the EU Clinical Trial Regulation by swiftly putting all necessary measures in place at the national level to successfully transition to this new regime.**

The role of ethics committees in clinical trials

The new EU Clinical Trial Regulation does not only bring improvements but also challenges due to significantly reforming the role of ethics committees in clinical trials. The differences between the old Directive and the new Regulation seek to create a more favourable environment to conduct clinical trials in the European Union. However, it is also feared that the role of ethics committees will weaken in at least some of the Member States because the new Regulation allows narrowing down the scope of ethics review.[24] A strong role of the ethics committee is paramount for the protection of the rights and safety of clinical trial participants. Member States are in the position to freely shape the scope of the ethical review. A careful balance between the faster approval procedures offered by the new Clinical Trial Regulation and high-quality ethics reviews not excluding the evaluation of the methodology and risks of a study needs to be found in order not to contribute to less protection of the participants.[25] **EAHP urges the Member States to ensure that the role of ethics committees under the new Clinical Trial Regulation remains strong in the interest of clinical trial participants.** Also, technical aspects should not be forgotten during the transition phase. Interfacing the new database with national systems is key for the smooth conduct of clinical trials.

[21] Tenti E, Simonetti G, Bochicchio MT, Martinelli G. Main changes in European Clinical Trials Regulation (No 536/2014). Contemp Clin Trials Commun. 2018 May 17;11:99-101. doi: 10.1016/j.conctc.2018.05.014. PMID: 30003173; PMCID: PMC6039537.

[22] Cagnazzo C, Campora S, Ferretti E, Arizio F, Marchesi E. New European Clinical Trial Regulation: perception and expectations in Italy. Ann Oncol. 2017 Jul 1;28(7):1648-1654. doi: 10.1093/annonc/mdx153. PMID: 28368461.

[23] Penlington M, Goulet P, Metcalfe B. Improving knowledge and trust in vaccines: A survey-based assessment of the potential of the European Union Clinical Trial Regulation No 536/2014 plain language summary to increase health literacy. Vaccine. 2022 Feb 7;40(6):924-933. doi: 10.1016/j.vaccine.2021.12.045. Epub 2022 Jan 5. PMID: 34996640.

[24] Lukaseviciene V, Hasford J, Lanzerath D, Gefenas E. Implementation of the EU clinical trial regulation transforms the ethics committee systems and endangers ethical standards. J Med Ethics. 2020 Dec 23:medethics-2020-106757. doi: 10.1136/medethics-2020-106757. Epub ahead of print. PMID: 33361396.

[25] Lanzerath D. Europäische Ethikkommissionen im Wandel: Herausforderungen durch neue Rahmenbedingungen [European ethics committees in transition: challenges of new requirements]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2019 Jun;62(6):697-705. German. doi: 10.1007/s00103-019-02952-8. PMID: 31069417.