Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria

SPECIAL ARTICLE
Bilingual edition English/Spanish

# Patient benefit as a goal of humanization

# El beneficio del paciente como objetivo de la humanización

Manuel David Gil-Sierra[1], María del Pilar Briceño-Casado[2], Eduardo López-Briz[3]

[1]Pharmacy Department, Hospital Universitario de Puerto Real, Puerto Real (Cádiz). Spain. [2]Pharmacy Department, Hospital Universitario de Jerez de la Frontera, Jerez de la Frontera (Cádiz). Spain. [3]Pharmacy Department, Hospital Universitari i Politècnic La Fe, Valencia. Spain.

**Author of correspondence**
María del Pilar Briceño Casado
Servicio de Farmacia
Hospital Universitario
de Jerez de la Frontera
Ronda de Circunvalación, s/n
11407 Jerez de la Frontera (Cádiz). Spain.

Email:
pilarbricenocasado@gmail.com

Received 5 December 2021;
Accepted 26 June 2022.
Early Access date (10/04/2022).
DOI: 10.7399/fh.13171

**How to cite this paper**
Gil-Sierra MD, Briceño-Casado MP, López-Briz E. Patient benefit as a goal of humanization. Farm Hosp. 2022;46(6):367-71.

## Abstract

Patient empowerment is one of the main pillars of humanisation. Therefore, consideration of patients' preferences and expectations should be taken into account during the practice of any healthcare professional. Improving overall survival and quality of life are the main wishes of patients. Indeed, the recent emergence of Patient Reported Outcomes has become an important focus for healthcare providers. The hospital pharmacist specialised in drug evaluation is a professional who evaluates the efficacy, safety, appropriateness and efficiency of treatments prescribed by physicians, and decision-making must be based on both technical factors and the four principles of bioethics. The correct application of evidence-based clinical practice allows to provide patients with increases in survival and/or quality of life, adapting the convenience and costs to the current situation. With this in mind, it could be said that the evaluation of medicines involves a strong commitment to humanisation. On the other hand, organisations that promote the rigorous evaluation and selection of medicines stand as allies of patients, as they have a direct impact on them and an indirect impact on society. Regulatory agencies in charge of approving and financing medicines in healthcare systems play a key role in the process of humanising clinical decision-making and empowering patients. If these agencies approve the use of new medicines based on data that do not measure quality of life or survival of patients when there are already other therapeutic alternatives for these pathologies, they are indirectly failing to meet patients' expectations and are infringing bioethical principles. This can have a considerable influence on the benefit-risk ratio of drugs, and

**KEYWORDS**
Patient; Humanisation; Patient-centered care; Empowerment; Bioethics; Evidence-based medicine; Drug evaluation.

## Resumen

El empoderamiento del paciente supone uno de los principales pilares de la humanización. Por ello, la consideración de las preferencias y expectativas de los pacientes debería ser tenida en cuenta durante el ejercicio de cualquiera de los profesionales de la salud. Mejorar la supervivencia global y la calidad de vida son los deseos principales de los pacientes. De hecho, la reciente aparición de los llamados *Patient Reported Outcomes* ha supuesto un importante foco para los agentes involucrados en la asistencia sanitaria. El farmacéutico hospitalario especializado en la evaluación de medicamentos es un profesional que evalúa la eficacia, seguridad, adecuación y eficiencia de los tratamientos prescritos por facultativos, y debe basar la toma de decisiones tanto en factores técnicos como en los cuatro principios bioéticos. La correcta aplicación de la práctica clínica basada en la evidencia permite proveer a los pacientes de incrementos de supervivencia y/o calidad de vida, adecuando la conveniencia y costes a la situación actual. Teniendo en cuenta esto, podría decirse que la evaluación de medicamentos supone un fuerte compromiso con la humanización. Por otra parte, las organizaciones que promueven la evaluación y selección de medicamentos rigurosamente se erigen como aliados de los pacientes, ya que repercuten de forma directa en éstos y de forma indirecta en la sociedad. Las agencias reguladoras encargadas de la aprobación y financiación de medicamentos en los sistemas sanitarios protagonizan un papel fundamental en el proceso de humanización de la toma de decisiones clínicas y empoderamiento de pacientes, ya que si aprueban el uso de nuevos medicamentos según datos que no miden la calidad de vida o supervi-

**PALABRAS CLAVE**
Paciente; Humanización; Atención centrada en el paciente; Empoderamiento; Bioética; Medicina basada en la evidencia; Evaluación de medicamentos.

patients may be treated with regimens that do not provide benefit, or may even harm them. Therefore, where should the process of humanisation be oriented? It seems reasonable that the benefit of the patient should be the fundamental objective of the process of humanisation of healthcare, evidently.

vencia de los pacientes cuando ya existen otras alternativas terapéuticas para estas patologías, indirectamente no estarán dando respuesta a las expectativas de los pacientes y conculcarán los principios bioéticos. Esto puede tener una considerable influencia en la relación beneficio-riesgo de los fármacos, pudiendo tratar a pacientes con esquemas que no aportan beneficio, o incluso podrían perjudicarles. Por tanto, ¿hacia dónde debiera ir orientado el proceso de humanización? Parece razonable que el beneficio del paciente sea el objetivo fundamental del proceso de humanización de la asistencia sanitaria, evidentemente.

Since Berwick first coined the concept of *triple aim* as the goal of excellence in healthcare (optimal clinical outcomes, lower costs, improved patient satisfaction)[1], humanization has become one of its main objectives[2-5]. The concept *humanization* affects a range of activities, some of which have not been clearly defined[6,7]. This lack of clarity hinders the implementation of measures that would enable patients to make their voice heard.

Patient empowerment is one of the main goals of humanization. At present, patient associations and companies (public and private) are making efforts to raise the visibility of this movement[8-10]. The *Guide for Humanization of the Spanish Society of Hospital Pharmacy* (SEFH) defines patient empowerment as one of the tenets of humanization[11]. Pharmacy Services have undertaken a wide variety of initiatives aimed at the humanization of their areas of activity[12-14]. However, many more programs/strategies are needed to adequately incorporate humanization into processes such as drug approval, regulation, evaluation, selection and monitoring. As demonstrated by some studies exploring the opinions of patients about therapeutic decision-making, healthcare professionals should consider patient preferences and expectations. Patients primarily aim at improving their overall survival and quality of life[15,16]. However, these endpoints are frequently neglected, which shows a failure to meet the principles of Beneficence and Autonomy. This is striking, especially in some types of cancer or rare diseases[17].

Whereas assessing survival in early stages of neoplastic or rare diseases with a long life expectancy is challenging due to the lack of data[18], evaluating quality of life is not an insurmountable obstacle. Hence, endpoints related to quality of life should be included in pivotal trials as a primary (or at least secondary) endpoint, which rarely occurs. Secondly, although quality-of-life data should be thoroughly interpreted, it is frequently mentioned briefly at the end of the "Results" section. For this reason, the recent emergence of the so-called *Patient-Reported Outcomes* (PROs) has become the focus of patients, scientific societies, researchers and the pharmaceutical industry[19-21]. This would involve the principles of Beneficence and Autonomy. To analyze these outcomes, it is necessary that healthcare professionals determine whether the endpoints assessed are clinically relevant and have been measured using validated instruments. Moreover, evaluators should avoid considering irrelevant findings that benefit external agents other than patients[22]. Additionally, patient opinions should be individually assessed and considered as a complementary –rather than substitute– element during clinical decision-making. An empowered patient would express his/her preferences for clinicians to take them into account for the selection of a drug therapy. This is especially relevant when several therapeutic options with similar efficacy but different safety profiles are available. This way, clinician's choice would be based on the aspects related to quality of life that will be most affected, and considering patient opinion. This would accomplish the principle of Autonomy. Likewise, an empowered patient has a better understanding of concepts related to clinical decision-making, efficiency and sustainability of the healthcare system. This would lead to greater equity in resource use and promote the bioethical principle of Justice.

The hospital pharmacist specialized in the evaluation and selection of medicines assesses the efficacy, safety, convenience and efficiency of the treatments prescribed by other physicians[23]. The work of these professionals has a transverse impact on other areas of the Pharmacy Service, such as Oncology or Outpatient Pharmacy. Clinical decision-making should not only be based on technical factors, but also on bioethical criteria[24-26]. Medical and pharmaceutical ethics evaluate interventions based on the four Principles of Bioethics: Beneficence, Non-Maleficence, Autonomy, and Justice[27,28]. There is a relationship between the technical criteria that determine the place of drugs in therapeutics and the fundamentals of bioethics. Thus, fulfillment of the principle of Non-Maleficence is guaranteed through the assessment of treatment efficacy and safety in clinical trials. This minimizes the possibility that patients receive an alternative therapy that may cause them an avoidable prejudice, favouring Non-Maleficence. On the other hand, the assessment of treatment appropriateness by drug evaluators would have a significant impact on patient Autonomy, since it favors the selection of therapies that minimize the number of visits to the hospital or have a more convenient route of administration. In this regard, patient opinion on the convenience of a treatment can be determining in decision-making. Finally, assessing the effectiveness of treatments guarantees compliance with the principle of Justice, since the rational use of medicines optimizes the use of resources of the healthcare system. This way, based on the concept of "cost-opportunity", the treatments with a lower economic impact would be used in some patients, without prejudice to the access of other patients to other therapies[29,30]. Otherwise said, it prevents wasting resources that are needed for other patients[31].

Drug evaluation is the first step in the process of disease management. An improper drug selection results in suboptimal outcomes being obtained in subsequent pharmaceutical interventions (i.e. pharmacotherapeutic or pharmacogenetic follow-up).

Taking the above into account, an appropriate drug selection certainly represents a strong commitment to humanization. The correct application of evidence-based clinical practice provides patients with treatments that improve their survival and/or quality of life. In addition, treatment convenience and costs are adjusted to each individual case, thereby meeting the three aims of Berwick. The creation of organizations and entities that promote a thorough and transparent evaluation and selection of medicines emerge as essential allies to patients[32]. Likewise, there are tools available for the adequate interpretation of data from clinical trials. These tools are based on objective criteria and enable correct therapeutic decision-making, which directly benefits patients and, indirectly, society[33,34]. This, however, collides with some situations in which the non-funding or restriction of medicines in certain clinical contexts is denounced, without further investigation of the reasons why these decisions are taken. An example is belantamab mafodotin in patients with refractory multiple myeloma, a drug that has been demanded by some organizations, but which benefit is unclear, with a cost yet unjustified[35,36].

Although not directly, regulatory agencies in charge of approving and financing medicines in healthcare systems play a key role in the process of humanising clinical decision-making and empowering patients. These entities, such as the European Medicines Agency (EMA) or the United States Food and Drug Administration (FDA) evaluate the scientific evidence currently available about the effects of drugs for specific indications[37,38]. Patient expectations are not met and some principles of bioethics are violated if these entities approve the use of new drugs based on clinical trial data for surrogate endpoints that do not measure quality of life or survival, when other alternative therapies are already available for these diseases. The assessment of surrogate endpoints in clinical trials is acceptable when there is an unmet need in a specific clinical setting where other drugs have not demonstrated a clinically relevant benefit, or when the patient has a good prognosis and the surrogate endpoints assessed correlate with final endpoints[39,40]. The approval of new drugs based on immature results that do not meet these criteria might result in a patient receiving a therapy under an inacceptable level of uncertainty. This may influence the benefit-risk balance of a drug significantly. Thus, some patients could be treated with schemes that do not provide any clinical benefit or that may compromise their health, thereby violating the principles of Beneficence and Non-Maleficence. A recent example is the use of the combination of olaratumab and

doxorubicin in soft tissue sarcoma[41], which marketing authorization was withdrawn due to an unfavorable benefit-risk balance.

Furthermore, accelerated access programs are being created to facilitate access to new medicinal products in clinical settings with unmet needs[42]. This very positive strategy, however, should be implemented with caution to prevent that entities authorize the use of new drug therapies based on interim data in diseases for which there is already a therapeutic option available[43].

Claims from patients for rapid access to new molecules could lead regulatory agencies to fail to complete the standard authorization procedures that guarantee the efficacy and safety of treatments. In this setting, a correct design of clinical trials assessing the efficacy and safety of new drugs represents a guarantee[44]. A limitation of single-arm clinical trials is that they complicate the inference of causality between the administration of the drug and the outcomes observed. This limitation is overcome in phase III trials thanks to patient randomization and use of a control arm[45,46]. In clinical trials, randomization prevents a potential misbalance of factors across patient cohorts. Additionally, it enables researchers to attribute clinical outcomes to a specific therapeutic intervention rather that to the natural course of the disease based on the characteristics of the patient. Therefore, data from single-arm studies (and their interpretation) are hardly generalizable to other populations.

A thorough drug evaluation also requires assessing its associated costs[47]. However, some regulatory medicines agencies such as the EMA do not assess the economic impact prior to approval of a new drug. This may pose a problem in the future, considering that the cost of some therapies, such as onco-hematologic treatments, has risen considerably in the recent times[48]. Although cost evaluation and humanization could be apparently unrelated, they are actually closely related. If the costs of new drugs –especially of those with a higher economic impact– are not assessed, there is a risk of underestimating the cost for the clinical benefit obtained or wasting resources, thereby limiting access of other patients to an adequate treatment[30]. Should healthcare humanization allow failing to treat a patient because all resources were used in another patient receiving a treatment with a high level of uncertainty? Certainly, the answer is *no*. It is essential that regulatory agencies, in collaboration with the pharmaceutical industry, are committed to avoiding this situation. In this line, the Directorate-General for Pharmacy and Health Products took a step forward and incorporated pharmacoeconomic studies in decisions involving Therapeutic Positioning Reports[49,50], which fulfils the principle of Justice.

Hospital pharmacists specialized in drug evaluation and positioning analyze new drugs and their potential role in meeting patient needs[23]. The technical criteria applied, such as efficacy, quality of life or safety, are intended to assess the extent to which a drug meets the primary needs of patients[51,52]. Indeed, the most important endpoints to which evaluators give more relevance are called *patient-centered endpoints* or *final endpoints* (i.e. overall survival or quality). Thus, these are the most frequently claimed endpoints in studies assessing patient empowerment and opinion[15,16]. A good understanding and interpretation of the methods used in studies (i.e. clinical trial design) is essential to associating the effect of treatments and facilitating therapeutic decision-making. Therefore, drug selection, technical criteria are not used as a goal, but as a means to meet patient needs, thereby fulfilling the four Principles of Bioethics.

As other fields, evidence-based clinical practice has evolved over the years. As a result, the selection and place of drugs in therapeutics should be adapted to continuous advances. However, changes in the terminology of processes should not overrule the know-how accrued from long experience. An example is the recent emergence of studies based on Real World Data[53], formerly called retrospective descriptive studies. Although the name of the concept has changed, its limitations persist[43,54]. A recent study revealed that Real Word Data studies conducted with EMA/FDA-approved drugs for the treatment of solid tumors had low quality and lower survival rates, as compared to pivotal clinical trials[54].

Both, the humanization process and evaluation of new drugs require the involvement of a multidisciplinary team[55,56]. Efforts should be made to raise awareness on humanization among all healthcare professionals involved in the selection, prescription and administration of drugs. The use of healthcare resources should be aimed at meeting patient preferences and expectations, which are focused on improving survival and quality of life[15,16]. Therefore, cross-level collaboration between centers were medicines are used and regulatory medicines agencies is essential[33,37,38]. This way, prior to the authorization and marketing of new molecules, the pharmaceutical industry should be required to provide further data about patient-centered endpoints.

Healthcare humanization has gained considerable relevance in the recent years. This movement has spread across almost all areas of hospital pharmacy, including pharmaceutical care or the dispensing of oncologic medicines to pediatric patients[57,58]. All these interventions are aimed at meeting patient needs and preferences. As mentioned above, patients primarily want to improve their life expectancy and quality of life[15,16]. This is also the main goal of drug evaluation. Therefore, humanization is a positive process that should always comply with the Principles of Bioethics (Beneficence, Non-Maleficence, Autonomy and Justice)[11,25,28]. As described above, these principles are closely related to basic criteria for drug evaluation (efficacy, safety, convenience and cost). Then, where should this new humanization process be directed to? The primary goal of any healthcare humanization process should be certainly aimed at achieving patient benefit.

## Funding

No funding.

## Conflicts of interest

Manuel David Gil-Sierra was a member of an advisory board of Janssen Pharmaceutica, and in simposia about onco-hematologic drugs marketed by Janssen Pharmaceutica and Pfizer. The rest of authors declare no conflicts of interest.

## Bibliography

1. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. Health Aff (Millwood). 2008;27(3):759-69. DOI: 10.1377/hlthaff.27.3.759
2. Herborg H, Soendergaard B, Froekjaer B, Fonnesbaek L, Jorgensen T, Hepler CD, *et al.* Improving drug therapy for patients with asthma--part 1: Patient outcomes. J Am Pharm Assoc (Wash). 2001;41(4):539-50. DOI: 10.1016/s1086-5802(16)31278-5
3. Cheng L, Sit JWH, Choi KC, Chair SY, Li X, Wu Y, *et al.* The effects of an empowerment-based self-management intervention on empowerment level, psychological distress, and quality of life in patients with poorly controlled type 2 diabetes: A randomized controlled trial. Int J Nurs Stud. 2021;116:103407. DOI: 10.1016/j.ijnurstu.2019.103407
4. Rubeis G. Guardians of humanity? The challenges of nursing practice in the digital age. Nurs Philos. 2021;22(2):e12331. DOI: 10.1111/nup.12331
5. Huber J, Karschuck P, Groeben C, Thomas C, Praus F, Miernik A, *et al.* Empowerment for our patients: Innovation in everyday urology. Urologe A. 2021;60(1):45-51. DOI: 10.1007/s00120-020-01415-2
6. Castro EM, Van Regenmortel T, Vanhaecht K, Sermeus W, Van Hecke A. Patient empowerment, patient participation and patient-centeredness in hospital care: A concept analysis based on a literature review. Patient Educ Couns. 2016;99(12):1923-39. DOI: 1016/j.pec.2016.07.026
7. Sandman L, Hofmann B, Bognar G. Rethinking patient involvement in healthcare priority setting. Bioethics. 2020;34(4):403-11. DOI: 10.1111/bioe.12730
8. Pino-Ramírez G. Empoderamiento, experiencia de vida y asociaciones de pacientes con Síndrome Ehlers-Danlos. Panamerican Journal of Neuropsychology. 2016;10:79-94. DOI: 10.7714/CNPS/10.4.206
9. Asociación de pacientes con EPOC. Guía para el empoderamiento del paciente con EPOC [internet]. 2021 [accessed 11/08/2021]. Available at: https://www.apepoc.es/epoc/guia-empoderamiento-del-paciente
10. iSanidad: lo mejor de la Sanidad. La AEMPS subraya la necesidad de crear un nuevo liderazgo para afrontar los desafíos de la farmacia hospitalaria [internet]. 2021 [accessed 11/08/2021]. Available at: https://isanidad.com/186737/la-aemps-subraya-la-necesidad-de-crear-un-nuevo-liderazgo-para-afrontar-los-desafios-de-la-farmacia-hospitalaria/
11. Álvarez Díaz A, Barreda Hernández D, Bermejo Vicedo T, Delgado Silveira E, García Martín A, García Palomo M, *et al.* Guía de humanización de la Sociedad Española de Farmacia Hospitalaria (SEFH) [Internet monograph]. Madrid:

Sociedad Española de Farmacia Hospitalaria; 2020 [accessed 06/08/2022]. Available at: https://www.sefh.es/guia-humanizacion/docs/guia-humanizacion-espanol.pdf

12. Redacción Médica. Farmacia de La Princesa crea el proyecto de humanización "Princesa en Casa" [Internet]. 2018 [accessed 06/09/2022]. Available at: https://www.redaccionmedica.com/autonomias/madrid/farmacia-de-la-princesa-crea-el-proyecto-de-humanizacion-princesa-en-casa-2453
13. Servicio de Farmacia del Hospital General Universitario Gregorio Marañón. Programa de Humanización 2020-2023 [internet]. 2020 [accessed 06/09/2022]. Available at: https://www.comunidad.madrid/hospital/gregoriomaranon/sites/gregoriomaranon/files/2021-03/PROGRAMA%20DE%20HUMANIZACI%C3%93N%20FARMACIA%20HGUGM%202021.pdf
14. Mar Gomis Pastor. Mhearth, "La salud móvil" al servicio de la humanización en el paciente trasplantado. Mesa Redonda Humanizar es Innovar, 64 Congreso Nacional de la Sociedad Española de Farmacia Hospitalaria. Sevilla; 2019 [accessed 06/09/2022]. Available at: https://www.sefh.es/eventos/64congreso/ponencias/58.pdf
15. Laryionava K, Winkler EC. Patients' preferences in non-curable cancer disease. Oncol Res Treat. 2019;42(1-2):31-4. DOI: 10.1159/000496120
16. Lo SH, Sharma R, Costentin CE, Aggio D, Shergill S, Colaone F, *et al.* Patient preferences for advanced hepatocellular carcinoma treatment: a multicountry stated preference study. Future Oncol. 2021;17(32):4275-87. DOI: 10.2217/fon-2021-0697
17. Gracia Guillén DM. Las enfermedades raras y la ética. Eidon: Revista de la fundación de ciencias de la salud. 2017;47:57-77.
18. Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, *et al.* Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018;378(6):518-28. DOI: 10.1056/NEJMoa1714678
19. Schoenbeck KL, Flynn KE. Health-Related Quality of Life of Patients with Chronic Myeloid Leukemia as Measured by Patient-Reported Outcomes: Current State and Future Directions. Curr Hematol Malig Rep. 2021;16(6):491-9. DOI: 10.1007/s11899-021-00656-y
20. Whitebird RR, Solberg LI, Ziegenfuss JY, Asche SE, Norton CK, Swiontkowski MF, *et al.* Personalized outcomes for hip and knee replacement: the patients point of view. J Patient Rep Outcomes. 2021;5(1):116. DOI: 10.1186/s41687-021-00393-z
21. Taliercio VL, Snyder AM, Biggs AM, Kean J, Hess R, Duffin KC, *et al.* Clinicians' perspectives on the integration of electronic patient-reported outcomes into dermatology clinics: a qualitative study. Qual Life Res. 2022;31(6):1719-25. DOI: 10.1007/s11136-021-03030-w
22. Bladh L, Ottosson E, Karlsson J, Klintberg L, Wallerstedt SM. Effects of a clinical pharmacist service on health-related quality of life and prescribing of drugs: a randomised controlled trial. BMJ Qual Saf. 2011;20(9):738-46. DOI: 10.1136/bmjqs.2009.039693
23. López-Briz E, Fraga-Fuentes MD, Clopés-Estela A, Ortega-Eslava A, Alegre-Del Rey EJ. Drug evaluation is also a clinical activity. Farm Hosp. 2020;45(1):45-7. DOI: 10.7399/fh.11560
24. Ruiz-Hornillos J, Hernández Suárez P, Marín Martínez JM, De Miguel Beriain I, Nieves Vázquez MA, Albert M, *et al.* Bioethical Concerns During the COVID-19 Pandemic: What Did Healthcare Ethics Committees and Institutions State in Spain? Front Public Health. 2021;9:737755. DOI: 10.3389/fpubh.2021.737755
25. Van Campen LE, Poplazarova T, Therasse DG, Turik M; Biopharmaceutical Bioethics Working Group. Considerations for applying bioethics norms to a biopharmaceutical industry setting. BMC Med Ethics. 2021;22(1):31. DOI: 10.1186/s12910-021-00600-y
26. Barreda Hernández D, Mulet Alberola A, González Bermejo D, Soler Company E. The reason for having a code of pharmaceutical ethics: Spanish Pharmacists Code of Ethics. Farm Hosp. 2017;41(3):401-9. DOI: 10.7399/fh.2017.41.3.10611
27. Beauchamp TL, Childress JF. Principios de ética biomédica. Barcelona: Masson; 1999.
28. Barreda Hernández D, Bellver Capella V, Del Moral García A, Díaz del Campo Lozano J, Francés Causape MC, González Bermejo D, *et al.* Código de Ética Farmacéutica [Internet monograph]. Madrid: Sociedad Española de Farmacia Hospitalaria; 2015 [accessed 06/08/2022]. Available at: https://www.sefh.es/sefhdescargas/archivos/Codigo_etico_final.pdf
29. Uyl-de Groot CA, Heine R, Krol M, Verweij J. Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe. Cancers (Basel). 2020;12(8):2313. DOI: 10.3390/cancers12082313
30. Herold Z, Szasz AM, Dank M. Evidence based tools to improve efficiency of currently administered oncotherapies for tumors of the hepatopancreatobiliary system. World J Gastrointest Oncol. 2021;13(9):1109-20. DOI: 10.4251/wjgo.v13.i9.1109
31. Organisation for Economic Co-operation and Development (OECD). Tackling Wasteful Spending on Health. Paris: OECD Publishing [internet]. 2017 [accessed 11/09/2021]. Available at: https://doi.org/10.1787/9789264266414-en
32. Ministerio de Sanidad, Consumo y Bienestar Social. Comisión Interministerial de precios de medicamentos y productos sanitarios [internet]. 2021 [accessed 11/09/2021]. Available at: https://www.mscbs.gob.es/profesionales/farmacia/CIPMyPS.htm
33. Ortega A, Fraga MD, Alegre-Del-Rey EJ, Puigventós-Latorre F, Porta A, Ventayol P, *et al.* A checklist for critical appraisal of indirect comparisons. Int J Clin Pract. 2014;68(10):1181-9. DOI: 10.1111/ijcp.12487
34. Gil-Sierra MD, Fénix-Caballero S, Abdel Kader-Martin L, Fraga-Fuentes MD, Sánchez-Hidalgo M, Alarcón de la Lastra-Romero C, *et al.* Checklist for clinical applicability of subgroup analysis. J Clin Pharm Ther. 2020;45(3):530-8. DOI: 10.1111/jcpt.13102
35. Ministerio de Sanidad del Gobierno de España. Acuerdos de la reunión de la comisión interministerial de precios de los medicamentos. Sesión 219 de 16 de diciembre de 2021 [internet]. 2021 [accessed 06/08/2022]. Available at: https://www.sanidad.gob.es/profesionales/farmacia/pdf/ACUERDOS_DE_LA_CIPM_219_web.pdf
36. Comunidad española de pacientes con mieloma múltiple. Falta de equidad en el Tratamiento del Mieloma Múltiple (Carta a la Ministra de Sanidad) [internet]. 2021 [accessed 06/08/2022]. Available at: https://www.comunidadmielomamultiple.com/falta-de-equidad-mieloma-multiple/
37. European Medicines Agency [internet]. 2021 [accessed 11/09/2021]. Available at: https://www.ema.europa.eu/en
38. U.S. Food and Drug Administration [internet]. 2021 [accessed 11/09/2021]. Available at: https://www.fda.gov/
39. U.S. Food and Drug Administration. Label of XPOVIO [internet]. 2019 [accessed 11/09/2021]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212306s000lbl.pdf
40. Agencia Europea del Medicamento. Blenrep® EPAR [internet]. 2021 [accessed 11/09/2021]. Available at: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-blenrep_en.pdf
41. Agencia Europea del Medicamento. Lartruvo® [internet]. 2021 [accessed 11/10/2021]. Available at: https://www.ema.europa.eu/en/medicines/human/referrals/lartruvo
42. National Institute for health and Care Excellence (NICE) Accelerated Access Collaborative [internet]. 2021 [accessed 11/10/2021]. Available at: https://www.nice.org.uk/aac
43. Garsen M, Steenhof M, Zwiers A. A Decade of Marketing Authorization Applications of Anticancer Drugs in the European Union: An Analysis of Procedural Timelines. Ther Innov Regul Sci. 2021;55(4):633-42. DOI: 10.1007/s43441-021-00260-5
44. Burns PB, Rohrich RJ, Chung KC. The Levels of Evidence and their role in Evidence-Based Medicine. Plast Reconstr Surg. 2011;128(1):305-10. DOI: 10.1097/PRS.0b013e318219c171
45. Spieth PM, Kubasch AS, Penzlin AI, Illigens BM, Barlinn K, Siepmann T, *et al.* Randomized controlled trials - a matter of design. Neuropsychiatr Dis Treat. 2016;12:1341-9. DOI: 10.2147/NDT.S101938
46. Vanderbeek AM, Ventz S, Rahman R, Fell G, Cloughesy TF, Wen PY, *et al.* To randomize, or not to randomize, that is the question: using data from prior clinical trials to guide future designs. Neuro Oncol. 2019;21(10):1239-49. DOI: 10.1093/neuonc/noz097
47. Ortega Eslava A, Marín Gil R, Fraga Fuentes MD, López-Briz E, Puigventós Latorre F (GENESIS-SEFH). Guía de evaluación económica e impacto presupuestario en los informes de evaluación de medicamentos [Internet monograph]. 2016 [accessed 11/10/2021]. Available at: https://gruposdetrabajo.sefh.es/genesis/index.php/component/content/?id=11&Itemid=13
48. Organización Mundial de la Salud. Technical report: pricing of cancer medicines and its impacts: a comprehensive technical report for the World Health Assembly Resolution 70.12: operative paragraph 2.9 on pricing approaches and their impacts on availability and affordability of medicines for the prevention and treatment of cancer [internet] 2018 [accessed 11/10/2021]. Available at: https://apps.who.int/iris/handle/10665/277190
49. Agencia Española de Medicamentos y Productos Sanitarios. Informe de Posicionamiento Terapéutico de tucatinib (Tukysa®) en el tratamiento de pacientes adultos con cáncer de mama HER-2 positivo, localmente avanzado o metastásico [internet]. 2021 [accessed 11/10/2021]. Available at: https://www.aemps.gob.es/informa/informes-de-posicionamiento-terapeutico/informe-de-posicionamiento-terapeutico-de-tucatinib-tukysa-en-el-tratamiento-de-pacientes-adultos-con-cancer-de-mama-her-2-positivo-localmente-avanzado-o-metastasico/
50. Agencia Española de Medicamentos y Productos Sanitarios. Informe de Posicionamiento Terapéutico de talazoparib (Talzenna®) en pacientes con cáncer de mama HER-2 negativo con mutaciones BRCA 1/2 en progresión a tratamientos previos [internet]. 2021 [accessed 11/10/2021]. Available at: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2021/IPT_32-2021-Talzenna.pdf?x95974

51. Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. J Clin Oncol. 2008;26(8):1355-63. DOI: 10.1200/JCO.2007.13.3439

52. Quinten C, Coens C, Mauer M, Comte S, Sprangers MAG, Cleeland C, *et al.* Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. Lancet Oncol. 2009;10(9):865-71. DOI: 10.1016/S1470-2045(09)70200-1

53. Gerdes S, Bräu B, Hoffmann M, Korge B, Mortazawi D, Wiemers F, *et al.* Real-world effectiveness of guselkumab in patients with psoriasis: Health-related quality of life and efficacy data from the noninterventional, prospective, German multicenter PERSIST trial. J Dermatol. 2021;48:1854-62. DOI: 10.1111/1346-8138.16128

54. Boyle JM, Hegarty G, Frampton C, Harvey-Jones E, Dodkins J, Beyer K, *et al.* Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study. Eur J Cancer. 2021;155:136-44. DOI: 10.1016/j.ejca.2021.07.001

55. Zheng Y, Ding X, Guo Y, Chen Q, Wang W, Zheng Y, *et al.* Multidisciplinary management improves anxiety, depression, medication adherence, and quality of life among patients with epilepsy in eastern China: A prospective study. Epilepsy Behav. 2019;100(Pt A):106400. DOI: 10.1016/j.yebeh.2019.07.001

56. Junta de Andalucía, Consejería de Salud y Familias. Comisión Central para la Optimización y Armonización Farmacoterapéutica [internet] [accessed 11/10/2021]. Available at: https://www.juntadeandalucia.es/organismos/saludyfamilias/consejeria/organos-colegiados/61450.html

57. Soler Company E, Barreda Hernández D. Editorial: Humanizando la atención farmacéutica desde la Farmacia Hospitalaria. Rev OFIL ILAPHAR. 2018;28(4):287-8.

58. Vall d'Hebron Barcelona Hospital Campus. Vall d'Hebron idea cajas con ilustraciones humanizadoras para cubrir los sueros de los pacientes pediátricos [internet]. 2021 [accessed 06/08/2022]. Available at: https://www.vallhebron.com/es/actualidad/noticias/vall-dhebron-idea-cajas-con-ilustraciones-humanizadoras-para-cubrir-los-sueros-de-los-pacientes-pediatricos