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SPECIAL ARTICLE

Clinical trials with . . . drugs? Based on 2 projects in Alzheimer's disease and malaria☆

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Abstract The biomedical research act (BRA) regulates clinical research in humans, but not that related to clinical trials with medicinal products. This article describes the scientific and regulatory foundations supporting 2 projects which could be observed as clinical trials, and can follow the BRA requirements. One is a positron emission tomography study with radiopharmaceutical to determine the presence of amyloid-β protein deposition in certain areas of the brain of cognitively healthy adults. The other is a study on controlled malaria infection in healthy volunteers using the inoculation of aseptic, purified and cryopreserved *Plasmodium falciparum* sporozoites. Since in both studies subjects undergo invasive procedures, the BRA requires the approval of the study by the relevant regional health authorities. These 2 studies have been the first ones that have used this regulatory procedure in Catalonia.

PALABRAS CLAVE
Ensayos clínicos;
Ley de investigación biomédica;
Regulación de la investigación clínica;
Enfermedad de Alzheimer;

Ensayos clínicos con. . . ¿medicamentos? A propósito de 2 proyectos en enfermedad de Alzheimer y paludismo

Resumen La ley de investigación biomédica (LIB) regula la investigación en seres humanos pero no la relativa a los ensayos clínicos con medicamentos. Este artículo describe los fundamentos científicos y normativos por los que 2 proyectos que pueden ser observados como ensayos clínicos pueden seguir los requerimientos de la LIB. Uno es el estudio de tomografía por emisión de positrones con radiofármaco para determinar la presencia de proteína β amiloide

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Tomografía por emisión de positrones;
Radiotrazador;
Proteína β amiloide;
Paludismo;
Esporozoitos asépticos

en ciertas áreas del cerebro de adultos cognitivamente sanos. El otro es un estudio de infección controlada de paludismo en voluntarios sanos, mediante la inoculación de esporozoitos de *Plasmodium falciparum* asépticos, purificados y criopreservados. En ambos estudios, al incluir procedimientos invasivos, la LIB exige la autorización del estudio por las autoridades autonómicas competentes. Estos 2 estudios han sido los primeros que han utilizado este procedimiento normativo en Cataluña.

The regulation of clinical research is continuously evolving and tends to increase in complexity. At times, the health authorities understand that certain clinical studies should be regulated by a pathway that can result in a reduction in the administrative burden for researchers. Below, we describe 2 projects with products that may be considered ''drugs'' but that were ultimately deemed otherwise. This led to both projects led to their administrative authorization through a different pathway than that of clinical trials (CT) with drugs. In fact, the Spanish Agency of Medicines and Healthcare Products (AEMPS) reached an agreement with the promoters to conduct the projects according to biomedical research act (BRA; Law 14/2007 of 3 July),[1] which permitted sidestepping compliance with the regulation on CT with drugs.[2] The 2 cases included an observational study on Alzheimer's disease (AD) and a study of controlled exposure to *Plasmodium falciparum* (*P. falciparum*) in healthy humans ''to standardize'' an *in vivo* model of the disease.

First case: observational study of Alzheimer's disease

Key aspects of Alzheimer's disease regarding the Alzheimer's and families study

The definition of dementia is based on diagnostic criteria[3] that, in AD, are *exclusively* clinical.[4,5] The progress in genetics, biochemistry, cell biology and neurosciences in the last 3 decades has changed the way we understand AD.[6] At present, AD is understood as a ''continuous'' process, from neurodegenerative changes in asymptomatic (preclinical phase) to the onset of cognitive impairment (prodromal phase) and the subsequent clinical condition of dementia.[7,8] The knowledge acquired from biomarkers (neuroimaging and amyloid-β [Aβ], tau and phosphorylated tau proteins in cerebrospinal fluid [CSF]) play a key role.[9] The earliest finding (preclinical phase) is the presence of amyloidosis in the brain (with retention of specific amyloid tracers for positron emission tomography [PET]) or in the CSF (with changes in the concentrations of Aβ, tau and phosphorylated tau proteins),[7,8] which may last more than 15 years before the onset of symptoms.[10] The use of biomarkers that reveal the state of the Aβ protein in an asymptomatic individual with AD is only considered in the framework of a research project.[7,8] It is this way because, without validation of the diagnostic criteria and their clinical predictive value in the preclinical phase,[11] individuals who are in this phase might *not* progress to AD over the course of their lives.[7]

The Alzheimer's and Families study (ALFA) is a longitudinal, long-term cohort study sponsored by and Pasqual Maragall Foundation. The study includes cognitively healthy (at baseline) children of patients with sporadic AD. Every 3 years, the participants perform various tests and procedures, including the PET determination of Aβ deposits in the brain. At the baseline visit, a lumbar puncture is performed to extract CSF. Using an Aβ PET, the volunteers are categorized as individuals with negative PET or positive PET (in the preclinical phase).[8] In this study, PET revealed whether the (asymptomatic) participant was accumulating Aβ in the brain. The function of PET is, therefore, physiological and is performed using an intravenous injection of a radiotracer.[12,13]

Spanish and European legislation: key aspects in connection with the assessment of a physiological clinical study with radiopharmaceuticals for positron emission tomography

Spanish legislation considers PET radiopharmaceuticals to be drugs for human use.[14,15] Since 2004, the criterion of AEMPS has been to consider that ''the administration of a radiopharmaceutical cannot be performed on a patient in the framework of a biomedical research project without the compliance of said project with legislation applicable to CTs''.[16] Nuclear medicine professionals, researchers, sponsors and clinical research Ethics Committees (ECs) accepted this criterion without evaluating in each case whether the study in question was or was not a CT that should be regulated by the specific legislation.[2] In any case, it is clear that studies using PET radiopharmaceuticals do not meet any of the characteristics required by the definition of a CT, nor does the radiotracer meet the characteristics of a ''research drug'' (Table 1).[2]

In 2008, AEMPS published a document of clarifications to the legislation on CTs.[17] The first issue was establishing whether a study was ''a CT with drugs''. The document provided an algorithm that showed that the ALFA study could not be considered a CT (Appendix Banexo 1). In addition, the European Union published a document[18] years ago clarifying the regulation of CTs.[19] *The document established that ''if the objective of the study is only a physiological characterization, in which PET is only used to study this, that is, there is no medicinal product that is the objective of the study, then the study is not a CT''*. These studies are not regulated by the European Union; it is the responsibility of each member state to decide whether and how to regulate them.[19]