Come cambia la ricerca clinica, e come i Comitati Etici la affrontano..

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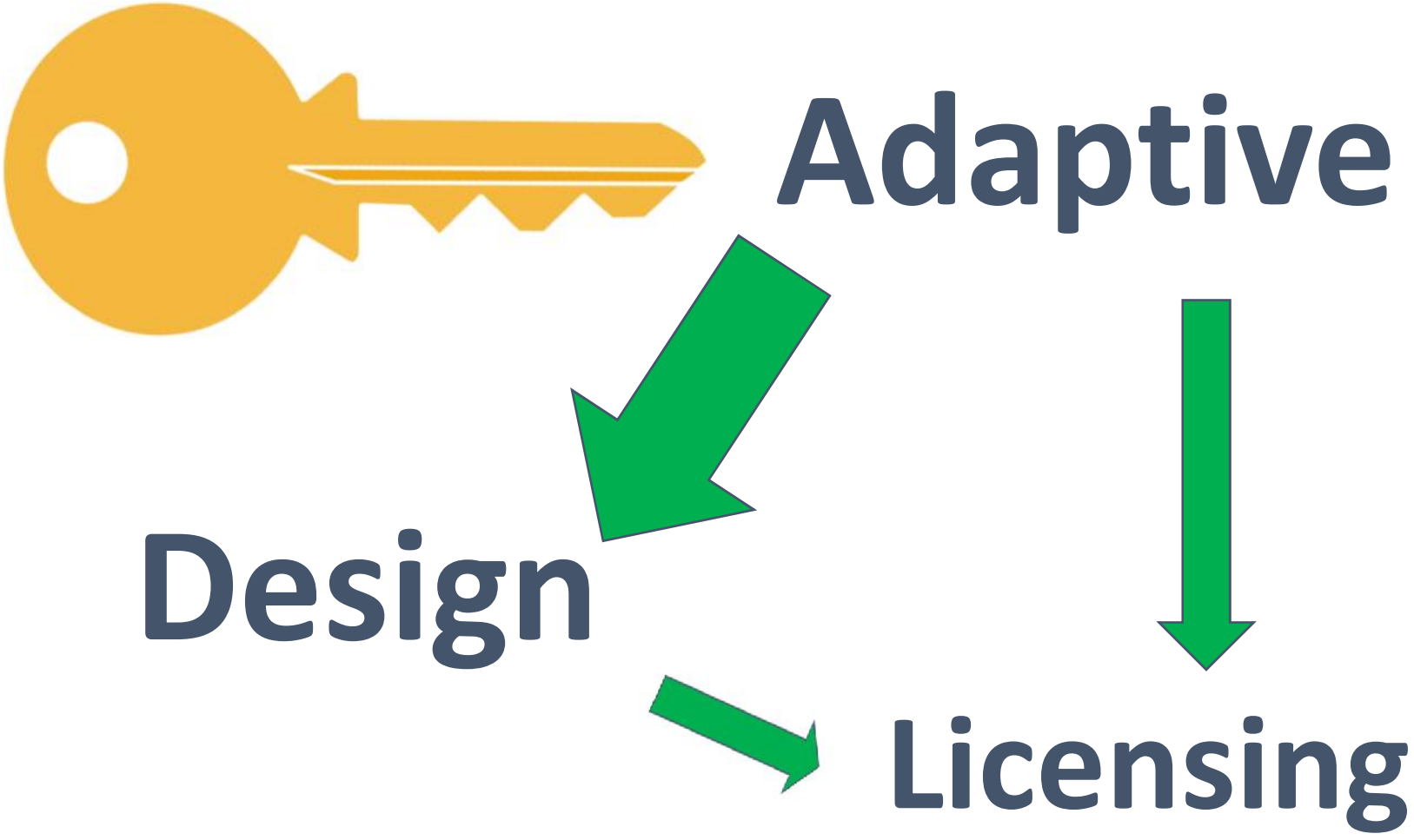
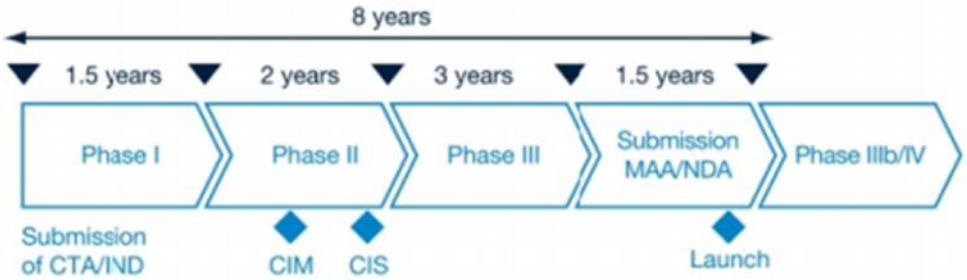
NUOVO REGOLAMENTO EUROPEO SULLA SPERIMENTAZIONE CLINICA:
A CHE PUNTO SIAMO E COSA BISOGNA FARE
Roma, 14 Novembre 2018


Adaptive
Design
Licensing

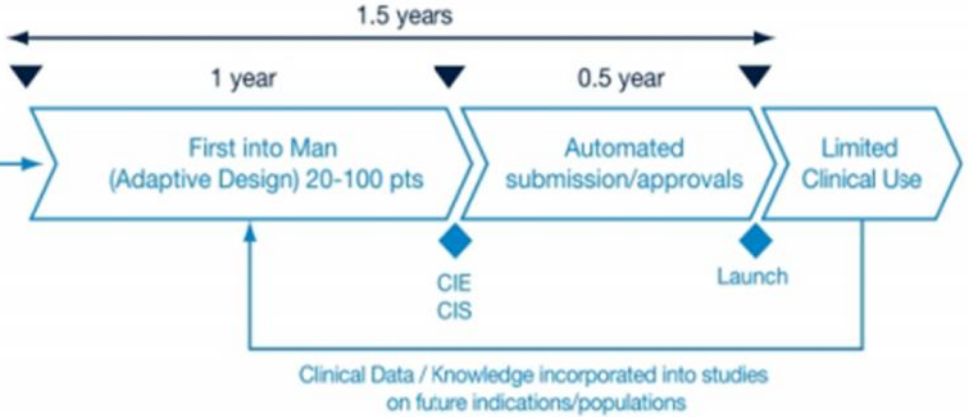


Oggi

CIM Confidence in Mechanism
CIS Confidence in Safety
IND Investigational New Drug
CTA CInical Trial Application
MAA Marketing Authorisation Application

2020

Confidence in Mechanism from Research work
Epidemiological Data
Disease Knowledge
Knowledge / Data from clinical usage or similar products
Proof of value requirements



Source: PricewaterhouseCoopers

European Medicines Agency

London, 18 October 2007
Doc. Ref. CHMP/EWP/2459/02

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN

In some instances studies can be planned with a so-called adaptive design involving design modifications based on the results of an interim analysis. Such a design has the potential to speed up the process of drug development or can be used to allocate resources more efficiently without lowering scientific and regulatory standards. This is especially welcome if at the same time the basis for regulatory decision-making is improved.

However, in a clinical development plan the purpose of phase III is to confirm the findings from pre-clinical studies, tolerability studies, dose-finding and other phase II studies (CPMP/EWP/2330/99). To argue for design modifications in a phase III trial (or a late stage phase II trial supposed to be part of the confirmatory package) is then a contradiction to the confirmatory nature of such studies and will be rarely acceptable without further justification: adaptive designs should not be seen as a means to alleviate the burden of rigorous planning of clinical trials.

BMJ Open

Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov

Laura E Bothwell, Jerry Avorn, Nazleen F Khan, Aaron S Kesselheim

Table 1 Definitions of types of adaptive designs[23]

Type of adaptive design	Definition
Adaptive dose-finding	These trials allocate patients to multiple different treatment doses and patient responses are assessed at interim analyses. Trial design is then adapted to allocate more patients to the treatment doses of interest, reducing allocation of patients to doses that appear non-informative. These studies usually occur in early-phase research to identify doses used in subsequent studies.
Adaptive hypothesis	A study design in which trial hypotheses are adapted in response to interim analysis results. For example, adaptive hypothesis trials could involve a preplanned shift from a single hypothesis to multiple hypotheses, preplanned switching between the null hypothesis and the alternative hypothesis or preplanned switching between the primary and secondary study endpoints.
Adaptive group sequential	In these variants on classical group sequential studies, results are analysed at interim analyses, with prespecified options of making adaptations such as sample size re-estimation, modification/deletion/addition of treatment arms, changing study endpoints, modifying dose and/or treatment duration or adapting randomisation schedules.
Adaptive randomisation	A study design in which accumulating results are observed and the randomisation scheme is adjusted so that patients enrolled later in the trial have a higher probability of being randomised to the treatment arm that was more effective among earlier patients in the trial.
Seamless Phase II/III	A study design that combines the objectives of the Phase II investigational stage with the Phase III efficacy or confirmatory stage into a single study protocol moving from one stage to the second stage without stopping the patient enrolment process.

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Table 1 Definitions of types of adaptive designs[23]

Type of adaptive design	Definition
Adaptive treatment-switching	A study design allowing the investigator to switch a patient's treatment from an initial assignment to an alternative treatment due to apparent lack of efficacy, disease progression or safety issues associated with the initial treatment.
Biomarker adaptive	This method allows adaptations to trial design based on interim analysis of the treatment responses of biomarkers, such as genomic markers. This design can be used to select patient populations for subsequent trials, identify the natural course of a disease, achieve early detection of a disease and/or help in developing personalised medicine.
Pick-the-winner/drop-the-loser	A study design that allows for dropping the inferior treatment group(s), modifying treatment arms and/or adding additional arms based on the review of accumulating data at interim analysis.
Sample size re-estimation	A study design using a flexible sample size adjustment or re-estimation based on interim analysis of accumulating data.
Multiple adaptive	This refers to a trial that incorporates multiple adaptive designs into a single study.

Bothwell LE, *et al. BMJ Open* 2018;**8**:e018320. doi:10.1136/bmjopen-2017-018320

Question time