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Evidence Notes

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Welcome to the sixth issue of *Evidence Notes*. Adaptive designs (ADs) have proliferated in recent years and are rapidly gaining acceptance with academia, the pharmaceutical industry and regulatory agencies as a means to improve clinical trial efficiency. Historically, ADs have largely been confined to studies in exploratory or early phase development. The aim of this current article is examine whether ADs are gaining traction with regulators as confirmatory trials, rather than exploratory research only. As with all our *Evidence Notes*, the aim is to provide a brief readable summary, rather than a lot of technical information. Please do consult the references provided for further information.

Admissibility of Adaptive Designs to Regulatory Agencies

Traditional drug development is expensive, often inefficient and may even result in a failure to achieve marketing authorisation[1,2]. This is because the successful outcome of these trials depends on the accuracy of ***estimated*** values for key design elements (e.g. expected differences between treatments). If these values are estimated inaccurately, then study failure, erroneous conclusions or trial inefficiencies may occur.

On the other hand, because adaptive designs (ADs) allow ***pre-planned*** modifications to key characteristics, based on accumulating data (see Table 1 for definitions & Table 2 for the range of items that can be prospectively modified), it is argued that they may improve trial efficiency (e.g., shorter duration, fewer patients) and reliability (e.g., improved optimal dose selection)[3,4,5]. The key features of an AD are:

1. Adaptions must be pre-specified & justified
2. The number of adaptions should be limited (e.g. studies with a large number of doses will be viewed sceptically)
3. Validity and integrity must be preserved

Table 1: Definition of Adaptive Designs

Body	Definition of Adaptive Design
PhRMA (non-regulatory)	A clinical study design that uses accumulated data to modify elements of the study as it continues ***without undermining the validity and integrity of the study***; changes should not be ad hoc but "by design"
EMA	A study design if, statistical methodology allows the modification of a design element (e.g. sample-size, randomisation ratio, number of treatment arms) at an interim analysis, with ***full control of the type I error***
FDA	A study that includes a ***prospectively planned*** opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.

Table 2: Potential Design Modifications from Draft FDA Guidance

	Adaptations
1	Eligibility criteria
2	Randomisation procedure
3	Treatment regimens (e.g., dose, schedule, duration)
4	Total sample size including early termination
5	Concomitant medications
6	Primary endpoint (e.g., which outcome assessment, which timepoint, unitary vs composite); NB. EMA states that a "change in the primary endpoint is difficult to justify"
7	Selection and/or order of secondary endpoints
8	Schedule of evaluations for data collection (e.g., number of timepoints, timing of last observation and duration of patient participation)
9	Analytic methods to evaluate endpoints (e.g., covariates, statistical methodology, Type I error control)

Despite their benefits, there is still a degree of caution in the widespread adoption of ADs, mainly due to a lack of final FDA guidelines, complexity of design (e.g. to avoid heightened risk of bias), and uncertainties around issues such as terminology, taxonomy, methodology & applicability. Despite this unfavourable picture, there is now a greater consensus on the "guiding principles" for their regulatory acceptance based on published outputs from EMA (2007 "reflection paper")[6], FDA (2010 draft guidelines)[7] and several other working groups, often with regulatory input[5, 8, 9, 10].

The regulatory position on the use of ADs in ***confirmatory trials*** can be summarised as follows:

1. The EMA categorise ADs according to traditional phases of drug development (phases I, II, III etc., or "exploratory" and "confirmatory" phases) and advise caution when considering the use of ADs in late phase II/III trials; such designs, though possible, will "rarely be acceptable without further justification".
2. The FDA do not specifically use terms such as "phase I, II or III" or "confirmatory study" but instead refer to ADs in "adequate and well-controlled effectiveness (A&WC)" trials. ADs are either "***well understood***" (e.g. adaptations in patient population, sample size, non-efficacy related outcomes, or early termination due to lack of efficacy etc.) or "***less well understood***" (e.g. unblinded sample size re-estimation or analysis of treatment effects, adaptations from an exploratory study with multiple doses/endpoints to an A&WC-type study, adaptive randomisation etc.). "Less well understood" studies are considered to be of higher risk as there is 'less regulatory experience in terms of drug approval'.

Though these documents establish a useful framework for understanding the regulatory position, they were published 5-8 years ago and what may have been "less well understood" at that time may be more acceptable now. Additional insights on the position of the Regulators may, therefore, be obtained by examining examples of ADs in ***confirmatory studies*** that have formed part of successful regulatory approvals. Though these are currently rare, a number of such studies have been identified[11, 12] and are described below. Where available, HTA comment on these adaptive study designs has also been provided.

Details of relevant examples are provided in Table 3 and a brief summary of key points from each is presented below in approximate chronological order as the regulatory opinion may have evolved over time:

1. Indacaterol was approved for use in Chronic Obstructive Pulmonary Disease (COPD) by EMA (2009) & FDA (2011) based, in part, on an adaptive "seamless" Phase IIB-III design in which multiple doses of Indacaterol were first tested vs placebo and then, based on interim data, confirmatory dose assessment was conducted (INHANCE study [13]). The relative contribution of this study to approval is difficult to assess due to the number of submitted studies: approval was based on 3 (EMA) & 6 (FDA) pivotal studies. FDA initially cautioned that such an adaptive study was risky with limited prior information and, in fact, an original application (based on the adaptive study & a phase III efficacy study) was deemed insufficient. In terms of HTAs, the INHANCE study was included

Table 3: Examples of Adaptive Designs in Pivotal Confirmatory Studies Which Have Formed Part of a Successful Regulatory Package

Drug	Indication	Adaptive Trial	Adaptation
Arcapta Neohaler (US); Hirobriz Breezhaler (EU); Indacaterol[13]	For treatment of airflow obstruction in patients with Chronic Obstructive Pulmonary Disease (COPD)	INHANCE: a randomized, D/B, D/D, multi-centre, adaptive, P/G study of indacaterol using blinded formoterol (12 µg b.i.d) and O/L tiotropium (18 µg o.d.) as active controls	A "seamless" Phase IIB/III design. Stage 1: indacaterol (4 doses) vs placebo and active controls (2 wks treatment). Stage 2: IDMC selected 2 doses for remainder of the study. After dose selection, patients continued on D/B treatment for up to 26 weeks.
Fulyzaq; crofelemer[15]	Symptomatic relief of non-infectious diarrhoea in adult HIV/AIDS patients on anti-retroviral therapy	ADVENT study: pivotal, confirmatory randomised, multi-centre, adaptive, D/B, P/C (4wks) & placebo-free (20wks)	A "seamless" phase IIB-III design. Stage 1: dose-selection (3 doses of crofelemer vs placebo); Stage 2: confirmatory (single dose) assessment (based on analysis of interim data by IDMC). All study procedures performed in Stage 1 and Stage 2 of the trial were identical and subjects participated in either Stage 1 or Stage 2, not both
Procysbi (cysteamine bitartrate, RP103); EU mercaptamine[16]	Management of nephropathic Cystinosis in Children ≥ 6 years and adults with nephropathic cystinosis	A 9-week, O/L, randomised, XO, multi-centre adaptive non-inferiority trial to evaluate the safety & efficacy of RP103 delayed release capsules vs Cystagon	Unblinded sample size re-estimation. The initial sample size was based on feasibility. The trial SAP called for a re-estimation of sample size once 20 evaluable patients completed the study. The re-estimation indicated that a total sample size of 36 patients was required.
Hemangeol (US); Hemangiol (EU); Propranolol[17]	Treatment of proliferating infantile hemangioma requiring systemic therapy in infants aged 5 wks to 5 months	Study 201: pivotal confirmatory, randomized, D/B, P/C, multiple dose, multi-centre, adaptive Phase IIB/III study in infants	A "seamless" phase IIB-III design. Stage 1: propranolol (4 regimens) vs placebo. Stage 2: one active dose vs placebo.

D/B = Double Blind; P/C = Placebo Controlled; O/L = Open Label; XO = Cross-over; D/D = Double Dummy; P/G = Parallel Group; SAP = Statistical Analysis Plan

in a NICE COPD evidence update (Feb 2012)[14]. They acknowledged the positive data from the study but made no specific comment on the AD.

2. In 2012 crofelemer became the first FDA approved product, based primarily on a ***single*** adaptive 2-stage, "seamless" phase IIB-III pivotal trial of non-infectious diarrhoea in HIV/AIDS patients on anti-retroviral therapy (the ADVENT study)[15]; (two supportive studies used a different primary endpoint & formulation). The design enabled efficacy data to be combined from both placebo-controlled stages. At the time of writing, it is unclear whether crofelemer has been submitted for EU approval; anecdotal information suggests that the EMA accepted the study design but requested another single dose study.
3. Procysbi was approved for the management of nephropathic cystinosis in children & adults by both FDA & EMA (2013) based on a single "adaptive" pivotal study[16] which used unblinded sample size re-estimation. According to FDA the trial design met regulatory requirements for A&WC trials (given that a blinded design was not feasible) and in EU the CHMP agreed the design was acceptable. However, nowhere in the FDA or EMA reviews is there any comment on the "adaptive" feature of the trial.
4. Hemangeol in infantile hemangioma was approved by both agencies in 2014 using a ***single*** pivotal "seamless" Phase IIB-III design based on recommendations made in parallel discussions with both FDA and EMA[17]. Despite approval, FDA made the following points:
   a. Because randomization to all treatment arms had completed before the interim… *"it is doubtful that the interim analysis was necessary…, or that a seamless Phase II and III adaptive design was required."*
   b. FDA advised adjusting the p-value to <0.01 to allow approval based on a single trial.

   In terms of HTA, a positive opinion was received from IGWIG (Dec 2014)[18]. NICE have not yet performed a technology appraisal and, although limitations of the design were raised in a NICE Medicines Evidence Commentary (April 2015)[19], these were not, however, to do with the adaptive approach but rather the selected patient population & dose.

In summary, successful regulatory approvals based on ADs in ***confirmatory studies*** are rare but are beginning to emerge. They appear to mostly involve "seamless" dose selection & assessment studies or those in relatively rare diseases. Thus, the above examples show that it ***is*** possible to conduct such trials for registration, even those that meet FDA criteria for "less well understood" designs, despite this being a higher hurdle. Future on-going studies (e.g. the state-of-the-art adaptive I-SPY- 2[20] oncology study developed in partnership with the FDA) may help broaden Regulatory experience and acceptability.

Further information on this subject can be found in the references provided.

Martin Jones & Paul Gandhi
Corresponding author:
martinjones@bridgemedical.org

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