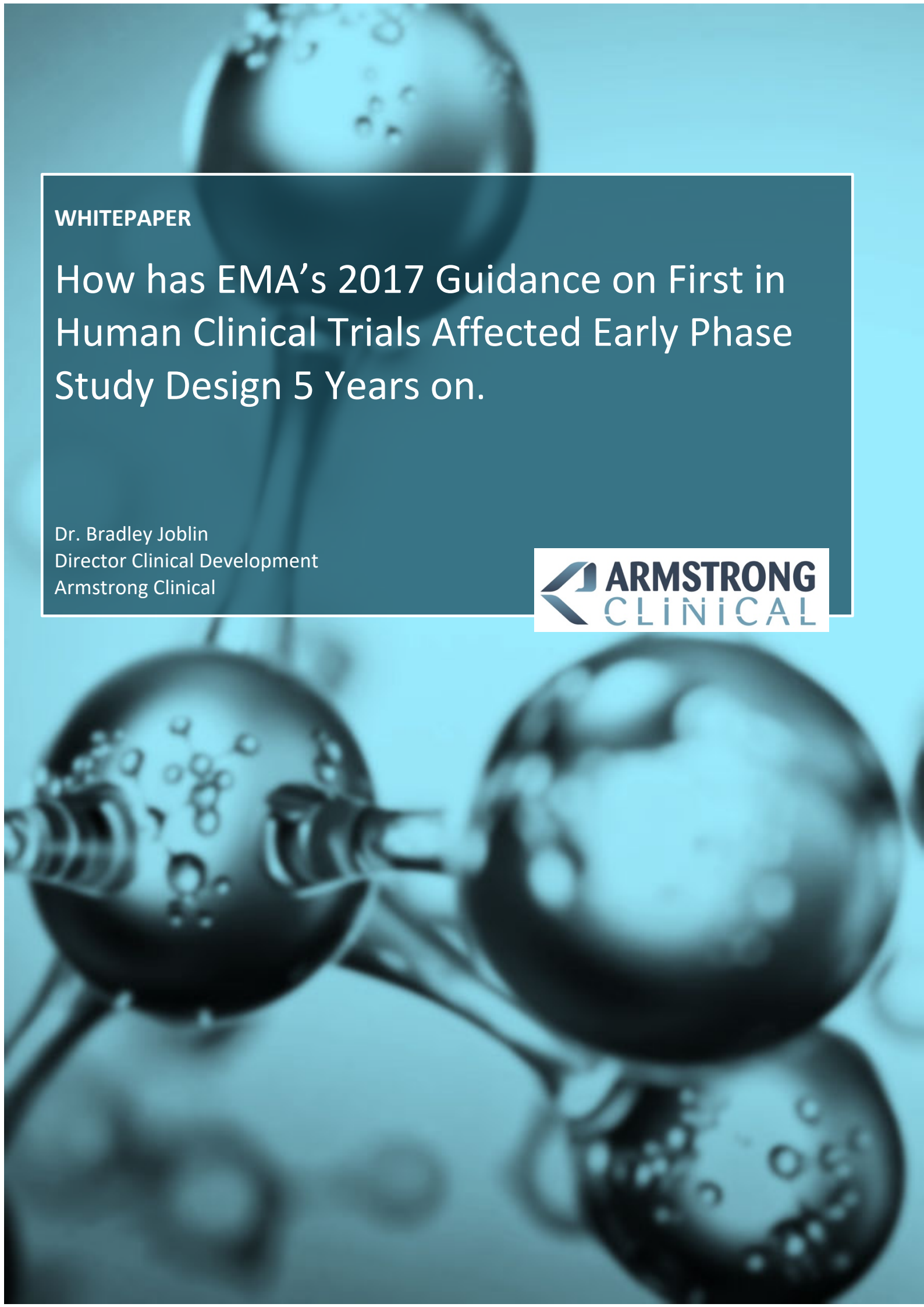

WHITEPAPER

How has EMA's 2017 Guidance on First in Human Clinical Trials Affected Early Phase Study Design 5 Years on.

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Introduction

"The expected exposure in humans at a dose to be given, in comparison to the exposure at which certain effects were observed in animals or earlier in the study in humans, is considered more relevant than the relative dose levels between animals and humans."

EMA FIH guidance 2017

In July 2017, the European Medicines Agency (EMA) revised its guidance on First in Human (FIH) Clinical Trials. The revised guidance described modern strategies to be incorporated into early-phase study design to help mitigate risks to participants on early-phase clinical trials, create efficiencies in study design and certainty in decision-making. Now, five years after its release, this whitepaper reviews the extent to which the strategies described in the 2017 EMA have been utilized in current early-phase studies. In addition, we look at specific design principles that were suggested and which have become commonly incorporated in recent FIH studies.

The 2007 vs 2017 EMA Guidelines

First-in-human (FIH) studies are critical initial investigations used to determine the safe dosing characteristics of a new investigational medicinal product. EMA's FIH guidelines were first released in 2007. These guidelines helped sponsors safely transition their discovery from non-clinical into early clinical development. Identifying risks to participants and mitigating those risks is a consistent theme in both of the 2007 and 2017 EMA FIH guidance documents.

EMA's initial 2007 guidance document provided calculations for initial doses to be administered in FIH studies. Strategies for subsequent dose escalations and intervals between doses were also described. During this time, early phase studies were designed as rigid single ascending dose studies followed by rigid multiple ascending dose studies. Typically, dose escalations in early-phase SAD and MAD studies were fixed and based on data collected at certain doses in relevant animal model studies. In a fixed study design approach, the key parameters determining a safe dose range are set regardless of what the data received during the study informs us about the accuracy of our hypothesis and assumptions. Such fixed dose escalation study designs can often result in many objectives not being reached, such as the highest dose cohort being dosed without the highest tolerated doses being attained. With such early phase designs, improper dose selection can been seen as a primary reason for many drug development failures.

In 2017, EMA adopted the first update to their 2007 FIH guidance. The 2017 EMA guidance asked us to consider new approaches when designing FIH studies particularly when targeting doses and

More Detail

dose ranges. Each suggestion reflected advancements in analytical technology, study design techniques, translational science, medical, physiological, and biochemical knowledge. Each of these advancements has contributed to early-phase study designs being able to more accurately and comprehensively decipher the relationship between the drug concentration in the body (exposure) and the observed safety and efficacy. In doing so, early-phase design studies can more precisely describe and predict an investigational therapy's exposure/effect (PK/PD) relationship. Collecting more effective, predictive, targeted data earlier in development allows greater confidence in earlier stop/go development decisions. When these decision are implemented before critically expensive phase IIb and III mean, we reduce costly attrition rates of later drug development, increase the amount we spend on therapies with the potential to reach the market and decrease the spend on those that don't.

The 2017 EMA Guideline and Evolution of Early Phase Designs.

Even before EMA released its 2017 guidelines, early-phase trial designs employed novel strategies to achieve study objectives more efficiently. A clear example of early phase design evolution is seen in modern early clinical study designs being more integrated to include multiple parts such as SAD/MAD/food effect and patient cohorts. The emerging integration of pharmacokinetic (PK), pharmacodynamic (PD) analysis with the support of rapid analytical turnaround, help enable integrated protocols combining different study parts to become a mainstay of early phase studies. The integrated trial approach allows more questions to be answered under one 'umbrella' design. One obvious benefit of combining proof-of-concept trials (IIa) with dose-finding trials (SAD/MAD) is the reduced time-to-market. A seamless transition between study phases, by eliminating the requirement to close down a trial after performing a final analysis and before opening a new trial protocolm, eliminates the "lost" time/" white space" between the end of one trial and the start-up of the next.

Even before 2017, many global pharmaceutical companies already commonly incorporated these strategies (Novartis since 2005, AstraZeneca 2011). However, EMA's release of the 2017 guidelines encouraged *all* companies entering FIH studies to utilize these design principles and incorporate adaptive designs and predictive (PK/PD) modelling into their early phase studies.

Early Phase Adaptive Designs

Adaptive designs are clinical trials incorporating pre-specified changes (dose, size, subject selection) in design or analyses guided by examination of the accumulated data at an interim point in the trial. We monitor the incoming data and modify the protocol based on our learning. As EMA mentions, *"The dose increment between two dose levels should be guided by the dose/ exposure-toxicity or the dose/exposure-effect relationship defined in the*

Continuous Reassessment

"Dose estimation should be based on state-of-the-art modelling (e.g. PK/PD and PBPK):"

EMA FIH guidance 2017

non-clinical studies and adapted following review of emerging clinical data from previous cohorts ". "The Feasibility to review and adapt the planned study design based on emerging clinical data should also be considered." The result of adapting doses while conducting the study is that more patients are likely to receive doses that work because doses with inadequate efficacy are adapted out. In addition, more precise information on the drug's exposure levels and effect on the body obtained early results in a greater chance that the IIb and Phase III confirmatory trials will be successful.

Not only can we make more precise, effective dose/exposure calculations, as noted by the U.S. Food and Drug Administration, adaptive design can "*provide a greater chance to detect the true effect of a product, often with a smaller sample size or in a shorter timeframe"*. In general, early-phase adaptive designs provide more information to enable knowledge-based decisions to make development more efficient, informative, and likely to demonstrate significant clinical effects of investigational products.

PK/PD Modelling

The second approach highlighted in the updated recommendations is the use of a model-based design. Model-based designs estimate the relationship between exposure/event (efficacy or toxicity) and assign exposure levels based on the statistical probability of seeing that event. The PK/PD-based models and simulation approaches recommended in the new guidelines emphasize precision when determining starting exposures, dose increments, maximal exposures, and adaptations. In the case of estimating exposures for NOAEL the new guidelines state: *"The exposures achieved at the NOAEL in the most relevant animal species used (which might not necessarily be the most sensitive species) should be used for estimation of an equivalent exposure for humans. Dose estimation should be based on state-of-the-art modelling (e.g. PK/PD and PBPK) and/or using allometric factors."*

To facilitate precision in dose predictions, models and simulations integrate data from different studies (e.g. in vitro pharmacological data, in vivo pharmacokinetic and even data from other compounds with the same mechanism of action). Additionally, as data is collected, knowledge is continuously updated, and dose/exposure prediction is continually informed and refined. As such, modelling and simulation is not only recommended for calculating starting exposures but also for dose increments, calculations of maximal exposures, and to inform adaptations. PK/PD modelling has become a powerful predictive tool to improve the translation of preclinical findings to early clinical studies and to increase efficiencies in early-phase development.

The continuous reassessment model is the 3+3 updated equivalent of the seamless I/IIa study described earlier. It is still a 3+3 design but integrates accumulated observed data in the trial as well as prior information from preclinical

Summary

studies, clinicians, and past studies, to recommend an exposure with an estimated Dose Limiting Toxicity risk closest to the Target Toxicity Level of the next cohort/patient. The model learns as the trial progresses and the data from every patient enrolled is included to recommend the best MTD estimate for the next patient. The benefit of the continuous reassessment model is not only efficiency and precision within the early phase study, but as compared to the rule-based 3+3 design, it will identify the recommended phase II dose more accurately.

The Impact of 2017 on Early Phase Study Designs 2022

Though it is well established that adaptive and model-based designs are generally superior to more outdated rule-based design, their uptake remains low. Armstrong Clinical's clients include Biotechnology Companies, Medtech Companies, Phase 1 Units, CRO's and Venture Capital with Biotech companies in their portfolio. Only 5-10% of clients that come to AC for design optimization have already included adaptive and modelling in their early-phase designs.

Our understanding of disease using data, technology and innovation has led to exponential developments in translational science in all phases of clinical development. The 2017 EMA guidelines on FIH studies highlighted the benefits of modern, adaptive design and modelling and simulation tools. This was partly to help guide all companies, large and small, to design early-phase studies with greater safety, precision and efficiency. Hopefully with the help of specialised early phase clinical development experts more companies will include adaptations and PK/PD modelling in their early phase designs.

Armstrong Clinical is a specialist early-phase study design consultancy that acts as a clinical development arm for clients looking to enter early-phase clinical development. With experience, knowledge and expertise, AC works with clients to integrate the statistical, regulatory, pharmacological, toxicological, scientific, and clinical aspects of early-phase clinical study design to ensure our client's early-phase studies are definitive, efficient, and effective for identifying early the true potential of their therapy.