European Federation of Pharmaceutical Industries and Associations

EFPIA's Position on the Acceptance of Innovative and Complex Clinical Trials by International Markets

Introduction

Innovative and novel therapeutic options are in great demand around the globe since they are essential in bringing significant health benefits to society and patients, especially in areas of high unmet medical need. Innovation in clinical trial design has transformed evidence generation in drug development these last few years. Indeed, there has been a significant focus on using innovative and complex clinical trials with the aim of increasing their effectiveness and efficiency whilst maintaining high quality data for regulatory decision making. As a result regulatory agencies have issued new guidelines or revisited existing ones while a number of collaborative initiatives have emerged to support the use of complex trials (see Annex for further details).

In Europe, the Clinical Trial Facilitation and Coordination Group (CTFG), a working group of the Heads of Medicines Agencies[1], in their Recommendation Paper *on the Initiation and Conduct of Complex Clinical Trials*[2] released in 2019, consider a clinical trial design complex if '*it has separate parts that could constitute individual clinical trials and/or if characterised by extensive prospective adaptations such as planned additions of new Investigational Medicinal Products or new target populations'*. These include but are not limited to enrichment designs, adaptive designs, master protocols, use of historical controls in clinical trials.

As *per* the FDA, complex innovative trial designs include; seamless trial designs, modelling and simulations to assess trial operating characteristics, the use of biomarker enriched populations, complex adaptive designs, Bayesian models and other benefit-risk determination, among others. This shows despite termed somewhat differently, the array of design options developers are more and more using with the *aim to develop more efficient strategies to assess the safety and efficacy of medicinal products earlier in the development process and to adapt innovative techniques that help make clinical trials more cost efficient and flexible, allowing innovators to advance new approaches to care* (S. Gottlieb - former FDA commissioner, 2018).

As drug development is by essence global, it is important to get regulators' acceptance beyond Europe and the USA, which is the aim of this position paper. It is important to stress that in their Position Paper[3] on Considerations for Regulatory Reliance[4], which is supported by EFPIA[5], IFPMA emphasises the reliance principles should also apply to medicinal products which have been developed using complex clinical trials. This position paper should also be read in conjunction with the EFPIA Clinical Expert Group Paper[6] on Complex Clinical Trials.

[1] https://www.hma.eu/
[2] https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf
[3] https://www.ifpma.org/resource-centre/ifpma-position-paper-assessment-reports-as-a-tool-for-regulatory-reliance/
[4] WHO defines **Reliance** as the act whereby the National Regulatory Authority (NRA) in one jurisdiction may take into account and give significant weight to – i.e., totally or partially rely upon – evaluations performed by another NRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others.
https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf
[5] https://www.efpia.eu/media/413586/position-paper-on-expedited-regulatory-pathways.pdf
[6] https://www.efpia.eu/media/547467/innovation-in-clinical-trial-design-a-review-of-the-clinical-trial-design-landscape.pdf

EFPIA recommendations for the acceptance of Complex Clinical Trials by International Markets

Regulators face significant challenges as treatments become more innovative and scientific development becomes more tailored. Aligned and science-driven regulatory standards provide assurance of quality, safety, and efficacy and are important in making treatments available in a timely fashion. Equally important are efficient regulatory pathways that enable good decision making and optimal use of limited agency and industry resources.

When a regulatory agency is considering a product that has already been approved by another agency, such as EMA or US FDA, addresses a medical need and for which approval may be based on the use of novel evidence generation tools and methods, the following should always be considered in order to expedite the approval and speed up the availability of the new therapy to local patients:

- Rely on the reference agency assessment obtained by complex clinical trials and perform an abbreviated review focussing on the applicability of the results to the local population and health care system, with consideration of ethnic factors where appropriate.

For agencies seeking to develop a complex clinical trial regulatory framework:

- Seek to harmonise national requirements with existing recommendations or regulatory pathways available globally for such trials;

- Provide engagement opportunity during drug development and review to discuss specific local requirements, if appropriate;

- Ensure appropriate resources, capacity and expertise for communication and support during product development and review.

Annex

Existing guidances and initiatives

Some Regulatory Authorities have already established regulatory pathways to optimise drug development through the use of complex clinical trials and are increasingly supporting the use of such trials. The acceptability of data from innovative and complex clinical trials is essential to allow new medicines, including personalised medicine to be available as treatment options for patients in great needs. There has been and there will be significant interactions between Industry, regulators and other stakeholders on guidelines, recommendations and best practices for the appropriate use of innovative clinical trial designs.

- In 2007, the European Medicines Agency (EMA) released a '*Reflection Paper*[7] *on Methodological Issues in Confirmatory Trials Planned with an Adaptive Design*'. In April 2009, EMA and EFPIA held a second workshop[8] on '*adaptive designs in confirmatory trials*', including seamless adaptive Phase II/III trials, with the objective to illustrate the application of "Good Adaptive Practices" through presentations and discussions of case studies. The workshop was also the opportunity for the FDA to share their draft guidance for medicines and biologics.. Also in 2010, the Japanese Pharmaceutical and Medicines Device Agency (PMDA) issued their own guidance[9] on the same topic.

- In 2016, the EMA organised a workshop on single-arm trials in oncology[10] to explore the views of various stakeholders groups and discuss the need for further regulatory guidance with the ultimate aim of optimising the development of new cancer treatments in situations where patients have no treatment option or where the conduct of standard trials with a comparative arm is difficult, such as in rare cancers or selected populations.

- In August 2018, FDA established a Complex Innovative Trial Design Pilot Meeting Program[11] to support the goal of facilitating and advancing the use of novel complex clinical trial designs. Also in 2018, FDA issued draft guidance on '*Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics*'[12].

- In 2017, in both Europe and the US, the use of extrapolation and modelling and simulation (M&S) was explored further in various fora and workshops together with PMDA and Health Canada and led in 2018 to the release of the EMA Reflection Paper[13] *on the use of extrapolation in the development of medicines for paediatrics*, and to the revision of the ICHE11(R1) paediatric guideline[14].

- More recently, in November 2019 an expert working group has been established by ICH to develop harmonised guidance and key principles for adaptive designs as detailed in their E20 Concept Paper[15].

In addition to regulatory guidance documents, a number of initiatives are exploring the concept of complex trial designs. Among them, the IMI EU-Pearl project and the EU FP7 ASTERIX project:

- Through the Innovative Medicine Initiative[16], known to be world's biggest public-private partnership in the life sciences, between the European Union (represented by the EU Commission) and the European pharmaceutical industry (represented by EFPIA), the IMI

[7] https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-methodological-issues-confirmatory-clinical-trials-planned-adaptive-design_en.pdf
[8] https://www.ema.europa.eu/en/events/european-medicines-agencyeuropean-federation-pharmaceutical-industries-associations-second-workshop
[9] https://www.sciencedirect.com/science/article/pii/S0924977X10001902?via%3Dihub
[10] https://www.ema.europa.eu/en/events/workshop-single-arm-trials-oncology
[11] https://www.fda.gov/drugs/development-resources/complex-innovative-trial-designs-pilot-program
[12] https://www.fda.gov/media/120721/download
[13] https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf
[14] https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf
[15] https://database.ich.org/sites/default/files/E20_FinalConceptPaper_2019_1107_0.pdf
[16] https://www.imi.europa.eu/

EU-PEARL project[17] which started in Nov. 2019 aims at setting up adaptive clinical trial platforms to allow multiple companies to test their candidate drugs simultaneously against a shared placebo group.

- The FP7 ASTERIX[18] is another example of a EU-funded research project that focused on the development of more efficient and effective research designs to study new drugs and treatments for rare diseases. The overall aim was to achieve more reliable and cost-efficient clinical development of treatments for rare diseases and to stimulate the search for treatments for these devastating and largely ignored diseases.

[17] http://www.eu-pearl.eu/
[18] http://www.asterix-fp7.eu/