1 31 October 2022
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3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper on platform trials

Agreed by Methodology Working Party	08 September 2022
Adopted by CHMP for release for consultation	31 October 2022
Start of public consultation	11 November 2022
End of consultation (deadline for comments)	31 January 2023

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Keywords	Platform trials, Trial design, Master Protocols, Multiplicity

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1. Introduction

Platform trials have become more common in the recent years. Currently, they are frequently seen in Scientific Advice and more rarely as part of Marketing Authorisation Applications. This is, however, likely to change during the coming years. They contain some unique, mostly methodological, aspects and it has become apparent that a reflection paper is needed to enable adequate planning of platform trials such that they can be used as pivotal trials.

The aim of the reflection paper is to complement existing guidance documents, e.g. on multiplicity and adaptive design, and not to replace or revise them.

2. Problem statement

Platform trials increase the complexity in planning, conduct and reporting of a clinical trial. A consolidated position to address these challenges is needed and will be outlined in the reflection paper. Firstly, the aim is to clarify terminology and introduce the key concepts. Secondly, we aim to describe the key methodological topics unique to platform trials and important design features to guide study planning and protocol development and, thereby, ensure that reliable effect estimates, adequate to support regulatory decision making, can be generated. Thirdly, the aim is to describe CHMP's position on the increased complexity and uncertainty in decision making related to confirmatory platform trials. Reasons for the increased complexity are multiple:

1) requirement for Type I error control at the level of a platform trial vs an individual comparison within the platform trial results into different operating characteristics;

2) design characteristics that may risk interpretability of the results because they may impact estimation and/or Type I error rate/increase uncertainty, e.g. use of non-concurrently randomised controls and changes in allocation ratio, and;

3) impact on external validity and potential bias resulting from e.g. the study population not remaining consistent over time and sequential dissemination of results.

For some of the aforementioned aspects it is possible to have a CHMP position, which will be outlined (such as point 1). Some are inherent to platform trials (such as introduction of new arms when the study is ongoing) and it will be discussed under which framework and constraints reliable results can be generated. Lastly, there are aspects that are frequently included in platform trials but are not needed by design (such as use of non-concurrent controls) and can result in violation of key principles of pivotal clinical trials (such as strict control of Type I error) and increased bias and/or uncertainty; it will be discussed whether this can be reasonable. To summarise, the aim is to describe under which concrete circumstances and methodological constraints platform trials are suitable for regulatory decision making.

3. Discussion (on the problem statement)

The following topics will be addressed:

- Terminology and key concepts;
- Description of key methodological topics unique to platform trials;
- CHMP´s position on increased complexity and uncertainty in decision making related to confirmatory platform trials.

The last topic will be divided into subtopics related to: 1) Type I error control, 2) design characteristics that increase uncertainty in treatment effect estimates and 3) bias. The aim is to describe under which concrete circumstances and methodological constraints platform trials are suitable for regulatory decision making.

4. Recommendation

The Methodology Working Party recommends drafting a reflection paper on platform trials taking into account the issues identified above.

5. Proposed timetable

Establishment of drafting group 12/2022, discussion at CHMP 12/2023, proposed date for release of draft guideline 03/2024, deadline for comments 06/2024, re-discussion in MWP 09/2024. Expected date for adoption by CHMP 12/2024.

6. Resource requirements for preparation

The core drafting group will be a writing team of four people. A wider group of six additional contributors is foreseen for discussion and review. The core drafting group will attend twice monthly meetings; the wider drafting group will convene monthly.

We anticipate a wider meeting during the development with the Methodology Working Party and its associated European Specialised Expert Community (ESEC) and designated identified stakeholders. A workshop with external stakeholders at the end of the guideline writing process will be essential.

7. Impact assessment (anticipated)

Platform trials are likely to play an increasingly important role in marketing authorisation applications in the future. It is anticipated that this document will improve planning of confirmatory platform trials by sponsors and lead to improved consistency in scientific advice and regulatory assessment.

8. Interested parties

We have identified the CHMP and the SAWP as the two main stakeholders that will be highly affected by this Reflection Paper. Other regulatory stakeholders, which will likely be affected differently, are the Emergency Task Force (ETF), the Committee for Advanced Therapies (CAT), the Paediatric Committee (PDCO), the Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Orphan Medicinal Products (COMP). All of the aforementioned stakeholders will be consulted prior to releasing the draft to the public.

The Reflection Paper will also benefit from the input of initiatives such as ACT EU and other regulatory agencies (FDA, MHRA, PMDA). It is planned that the draft Reflection Paper will be discussed at a Biostatistics Cluster meeting to obtain feedback.

9. References to literature, guidelines, etc.

CPMP/EWP/908/99: "Points to consider on multiplicity issues in clinical trials"

CHMP/EWP/2459/02: "Methodological issues in confirmatory clinical trials planned with an adaptive design"

83 CPMP/ICH/363/96: ICH E9 “Statistical Principles for Clinical Trials”

84 CPMP/ICH/364/96: ICH E10 “Choice of control group in clinical trials”

85 EMA/298712/2022: “Complex clinical trials – Questions and answers”, Version 2022-05-23