Randomised Controlled Trials (RCTs) are the gold standard: Are they always used?

HPR169

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Objectives

RCTs are the cornerstone of medical research, providing strong validity through randomization and control of confounding factors[1]. However, they may be impractical in contexts with ethical constraints, high costs and lengthy timelines. This study analyses RCT use among approved orphan and oncology drugs between 2022 and 2024[2].

Methods

This analysis included 124 new active substances approved by the European Medicines Agency. Four were excluded due to their non-therapeutic nature or lack of clinical trials. Among the 120 drugs analysed, 123 pivotal studies were identified, as three products had two distinct trials. Each study was classified by phase, randomization, and control (placebo, standard of care, or uncontrolled). Subgroup analysis was performed on orphan drugs (n = 42) and non-orphan oncology drugs (n = 27) including onco-haematological ones.

DATASET COMPOSITION

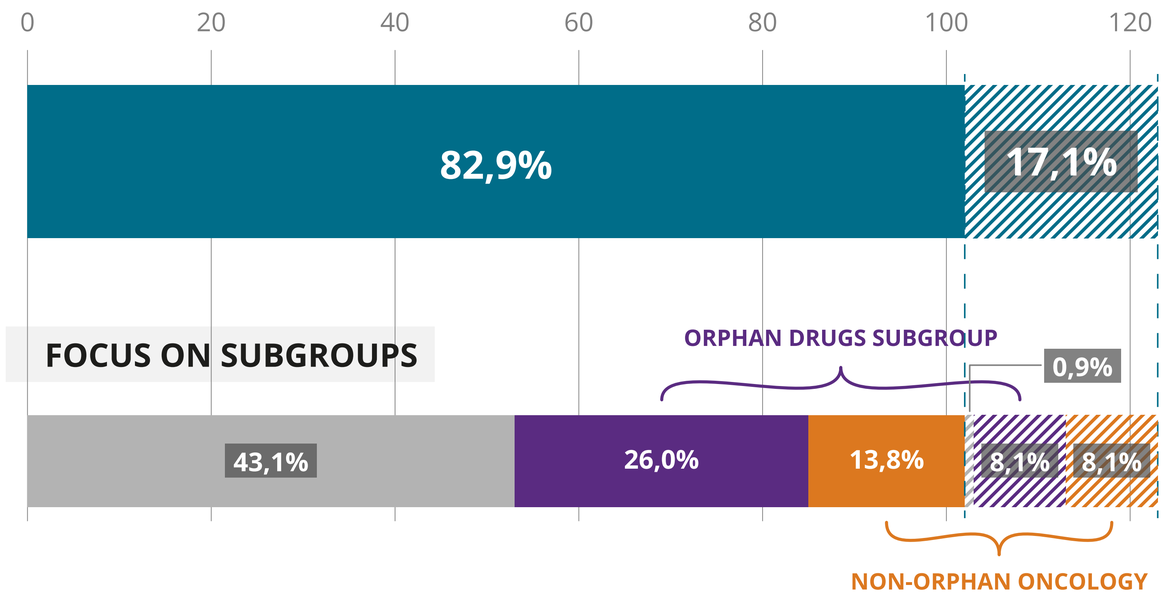
124 N° new active substances (NAS) approved by EMA

2022 2024 Approval period

4 N° excluded NAS due to their non-therapeutic nature or lack of clinical trials

123 **N° pivotal studies analyzed**

PHASE III DISTRIBUTION



TOTAL STUDIES
N° studies: **123**
N° Phase III studies: **102**
N° Phase II studies: **21**

SUBGROUPS
ORPHAN DRUGS SUBGROUP
N° studies: **42**
N° Phase III studies: **32**
N° Phase II studies: **10**

NON-ORPHAN ONCOLOGY & ONCO-HAEMATOLOGICAL DRUGS SUBGROUP
N° studies: **27**
N° Phase III studies: **17**
N° Phase II studies: **10**

OTHER DRUGS
N° studies: **54**
N° Phase III studies: **53**
N° Phase II studies: **1**

LEGEND

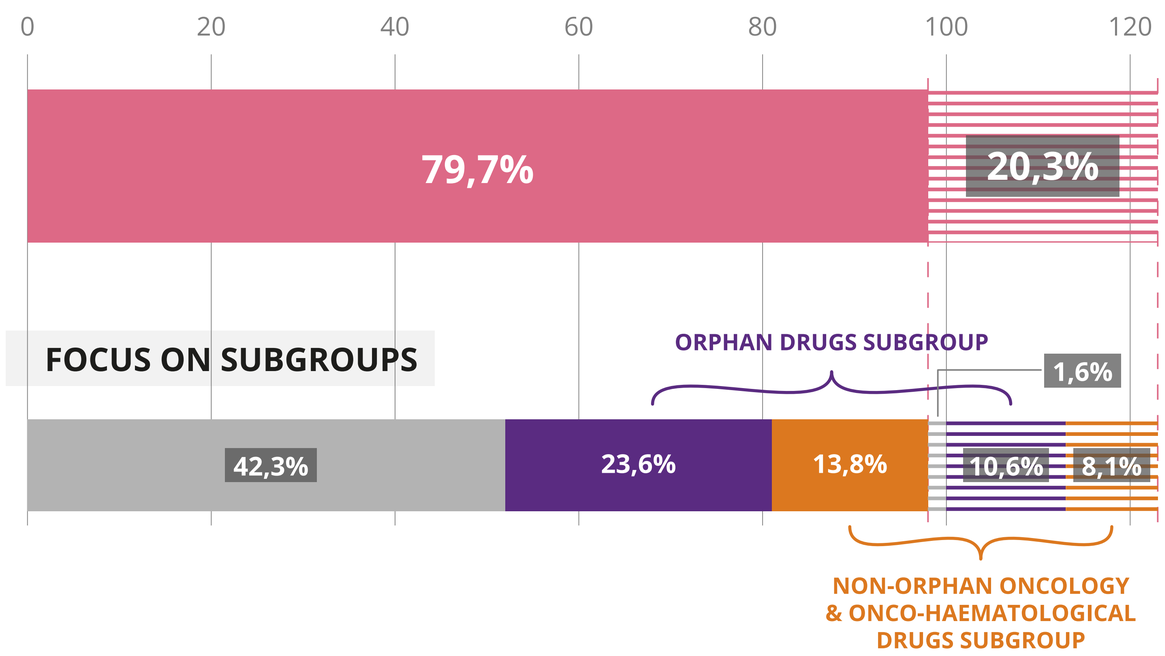
- **Phase III**
- **Phase II**
- **RCT studies**
- **Non RCT studies**
- **Orphan drugs**
- **Non orphan oncology & onco-haematological drugs**
- **Other drugs**

Total Studies: All pivotal studies identified for the analysed drugs.

RCT Studies: Randomised Controlled Trials, in which participants are randomly assigned to intervention or control groups to minimise bias.

Non-RCT studies: Other studies including uncontrolled trials or non-randomised studies (e.g., single-arm designs).

DISTRIBUTION OF RCTs



TOTAL STUDIES
N° studies: **123**
N° RCT studies: **98**
N° Non-RCT studies: **25**

SUBGROUPS
ORPHAN DRUGS SUBGROUP
N° studies: **42**
N° RCT studies: **29**
N° Non-RCT studies: **13**

NON-ORPHAN ONCOLOGY & ONCO-HAEMATOLOGICAL DRUGS SUBGROUP
N° studies: **27**
N° RCT studies: **17**
N° Non-RCT studies: **10**

OTHER DRUGS
N° studies: **54**
N° RCT studies: **52**
N° Non-RCT studies: **2**

APPROVAL TYPE ANALYSIS FOR UNCONTROLLED AND NON-RANDOMIZED STUDIES

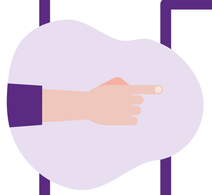
ORPHAN DRUGS SUBGROUP
- **3** Full
- **7** Conditional approval
- **3** Exceptional circumstances

NON-ORPHAN ONCOLOGY & ONCO-HAEMATOLOGICAL DRUGS SUBGROUP
- **1** Full
- **9** Conditional approval

OTHER DRUGS
- **1** Full
- **1** Withdrawn

Results

RCTs accounted for 79.7% of all studies (98/123). The proportion was lower among orphan drug studies (69.0%, 29/42) and non-orphan oncology studies (63.0%, 17/27). Conversely, the proportion of uncontrolled and non-randomized studies was higher in these subgroups: 31.0% (13/42) in orphan drug studies and 37.0% (10/27) in non-orphan oncology studies, compared to 20.3% (25/123) in the dataset. Notably, among these, 7 of the 13 orphan drugs and 9 of the 10 oncology drugs received conditional marketing authorisation, while 3 of the orphan drugs were authorised under exceptional circumstances. Considering study phases, Phase III trials were predominantly represented (82.9%, 102/123), although their frequency was lower in orphan drug studies (76.2%, 32/42) and non-orphan oncology studies (63.0%, 17/27).



Conclusions

RCTs remain the gold standard for evidence generation, the results show that they are not always conducted. This reflects flexibility in study design when RCTs are not feasible, particularly in orphan and oncology areas. However, rigor is maintained as 53.8% of orphan drugs and 90% of oncology drugs without RCT support must still provide additional evidence under conditional approval.

References

1. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. BJOG. 2018 Dec;125(13):1716. doi: 10.1111/1471-0528.15199. Epub 2018 Jun 19. PMID: 29916205; PMCID: PMC6235704.
2. European Medicines Agency (EMA). (2024). CHMP meeting highlights.

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