Evaluating early-stage oncology clinical trials in the era of Project Optimus: a scoping review

Marie-Karelle Riviere[1], **Anaïs Andrillon**[1,2], **Pavel Mozgunov**[1,3], **Emma Gerard**[4], **Moreno Ursino**[5]

anais.andrillon@saryga.com

[1] Department of Statistical Methodology, SARYGA, France

[2] ECSTRRA, INSERM U1153 CRESS, France

[3] MRC Biostatistics Unit, University of Cambridge, UK

[4] Statistical Innovation Hub, SANOFI, France

[5] HeKA, UMRS 1346, Inserm, Inria, Université Paris Cité, France

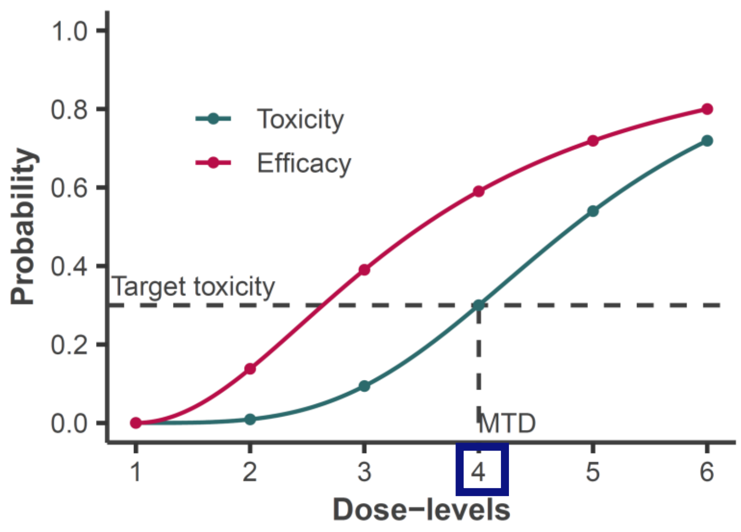
Inserm Université Paris Cité UKRI MRC Biostatistics Unit sanofi

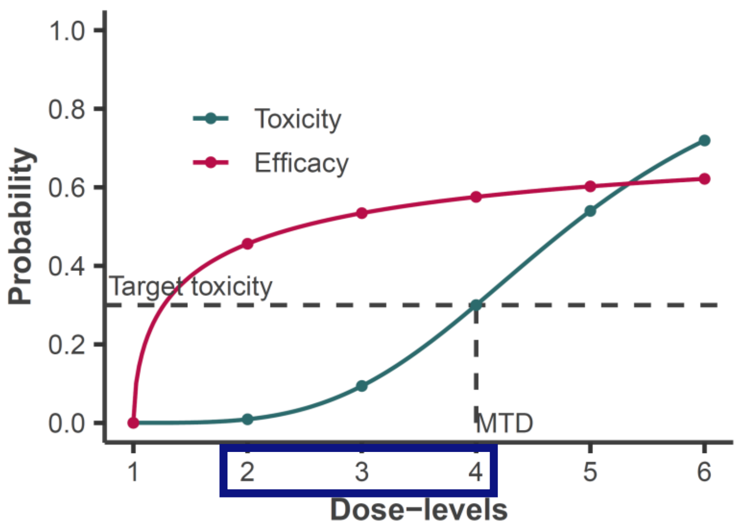
SARYGA STATISTICS & METHODOLOGY

On the importance of finding the optimal dosage…

Dosage considerations for the full development

- Doses and schedules of new agents may be inadequately characterized before initiating registration trials
- Too high dosage may bring safety concerns, potentially leading to an efficacious compound not entering into market
- Wrong dosing regimen may decrease the efficacy





More is not necessarily better and sometimes less is definitively better…

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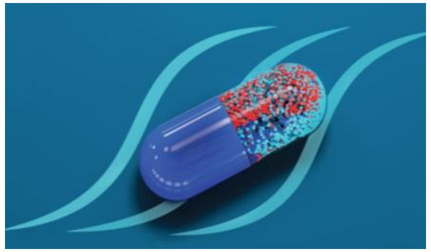
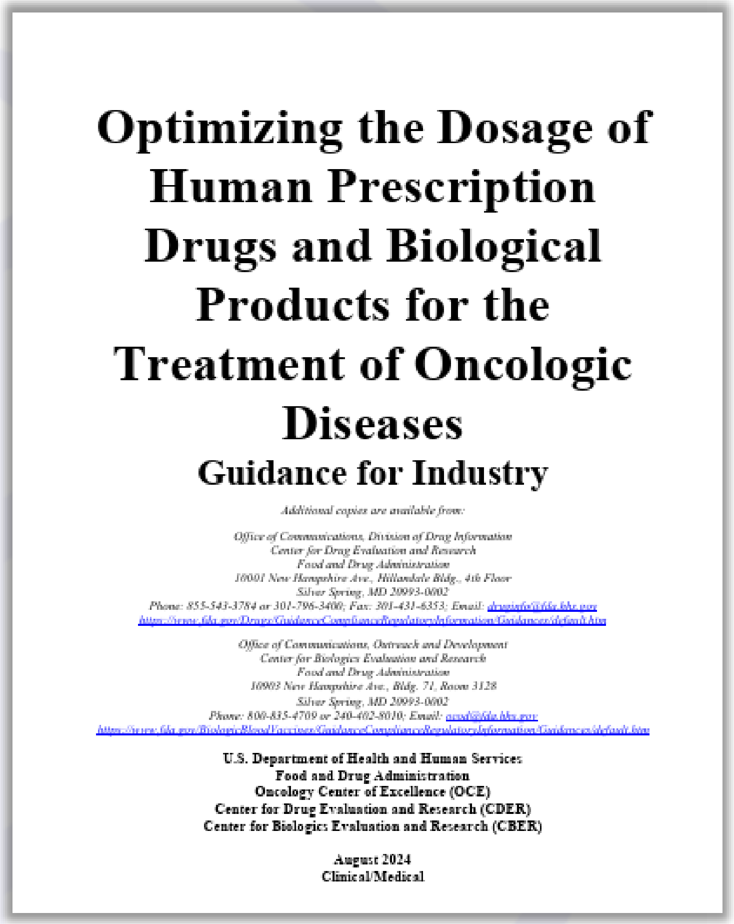
FDA's Project Optimus





Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Office of Communications, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2024
Clinical/Medical

Initiative to reform the dose optimization and dose selection paradigm in oncology

- Panel including medical oncologists, clinical pharmacologists, statisticians from academia, industry, and regulatory agencies

Dosages selection should be adequately supported by

- Safety (lower grades & late onset AEs, PROs)
- Efficacy/Activity/Biomarker
- Dose-exposure-response (PK/PD)

Favor early and comprehensive multiple dose regimen exploration during the clinical development

Comparison of 2 or more doses

LITERATURE REVIEW IN EARLY PHASE ONCOLOGY

What has already been done, and what could be improved in light of the Optimus recommendations?

335 statistical journals extracted from SCOPUS

- ***Statistical and mathematical journals*** *in English that accept submissions on biostatistical topics*

- 181 journals (Out of scope / Not in English)

+ 6 medical journals included addressing biostatistical aspects

160 journals finally retained for scoping review

880 papers extracted with keyword from SCOPUS and PubMed

Published between ***Jan. 1990 and Sept. 2023***

- 270 papers (duplicated, application of real trials, out of scope)

+ 31 papers from non targeted journals based on bibliographies

641 papers in total identified for scoping review

Keywords used for the research

Phase 1 OR Phase I OR phase I-II OR phase I/II OR phase 1-2 OR phase 1/2 OR Dose finding OR Dose-finding	AND	Oncology OR Cancer OR Maximum tolerated dose Toxicity OR Dose escalation OR Dose-escalation

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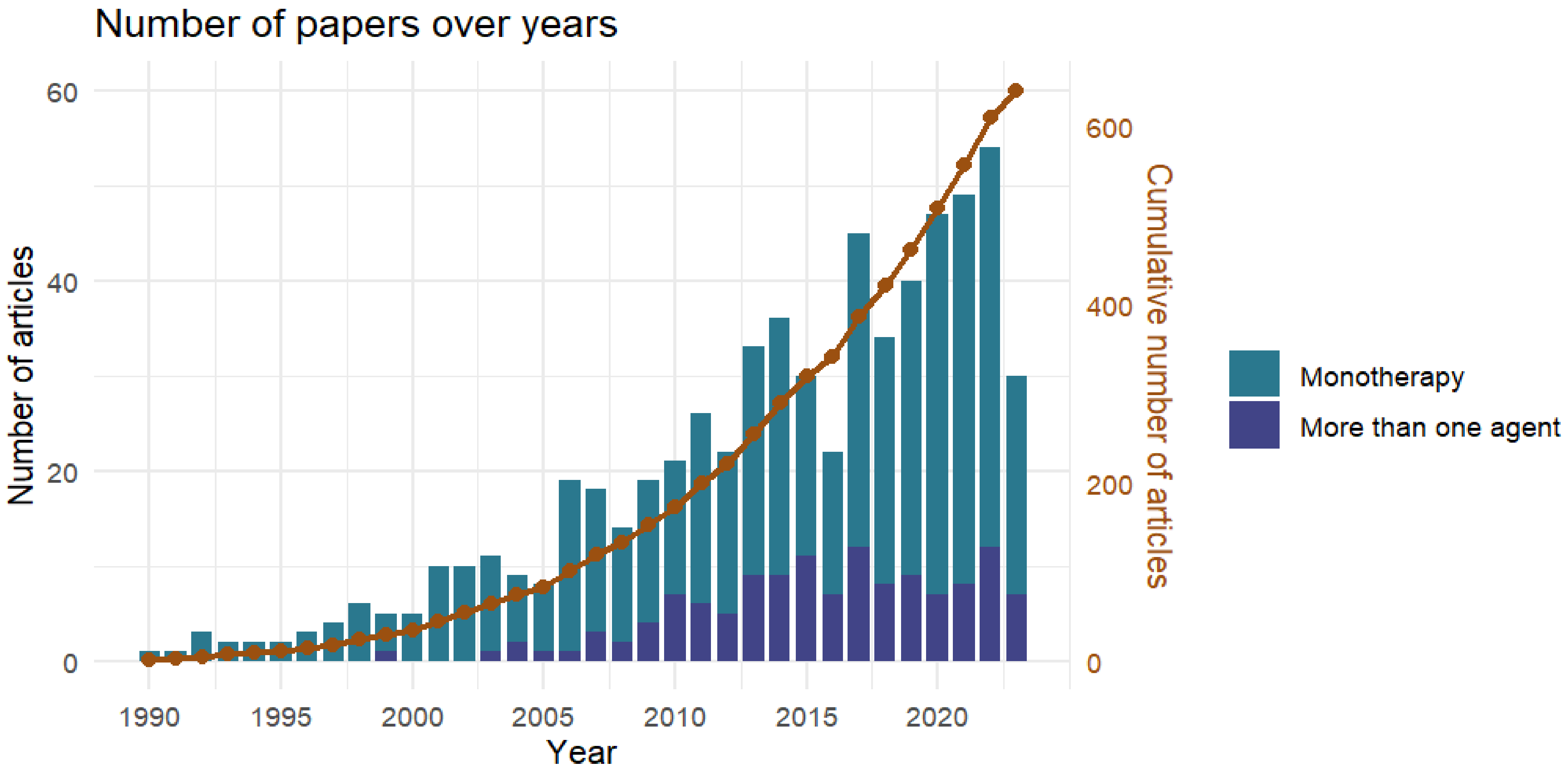
METHODOLOGY CONTRIBUTION OVER THE YEARS



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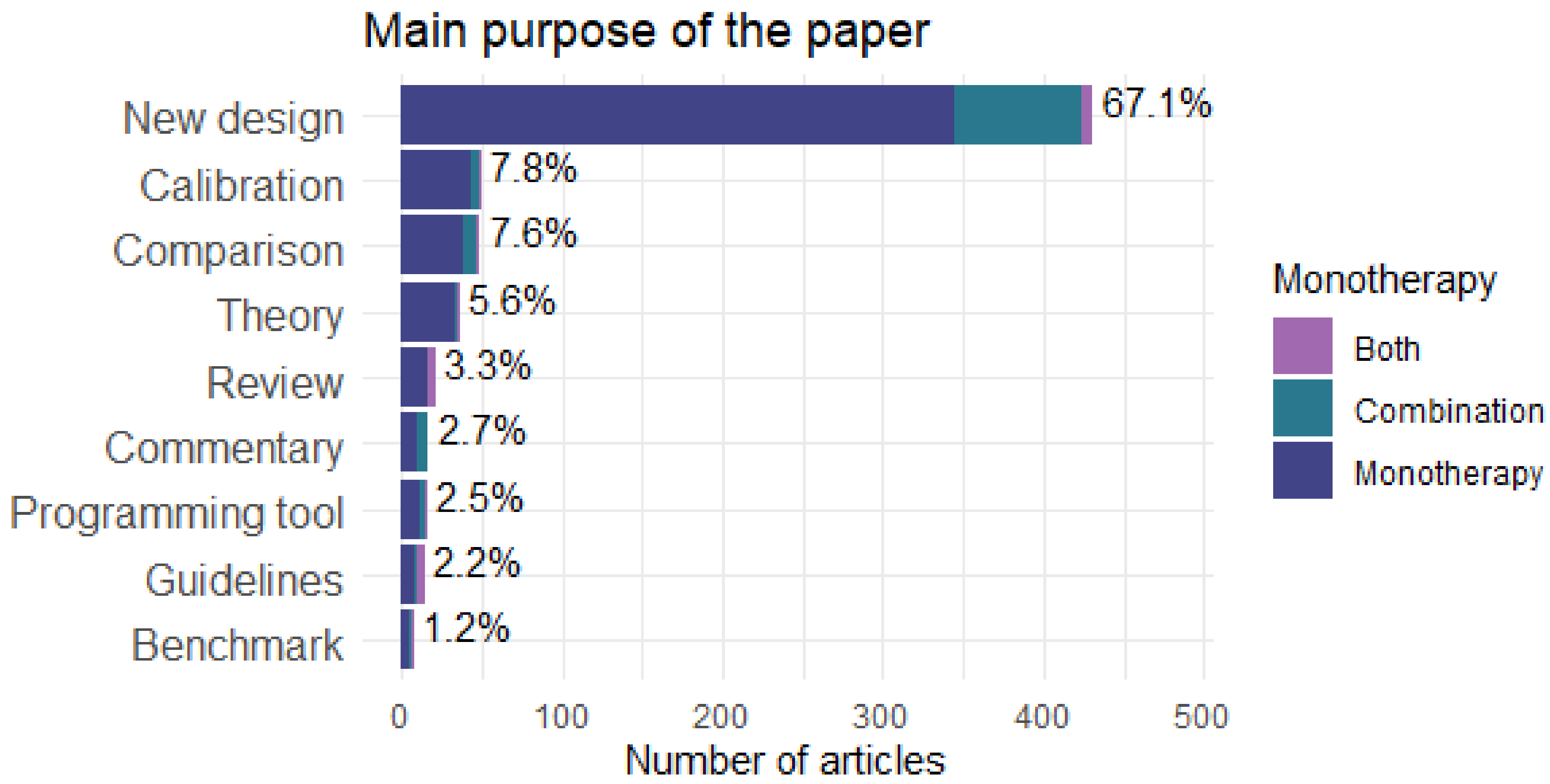
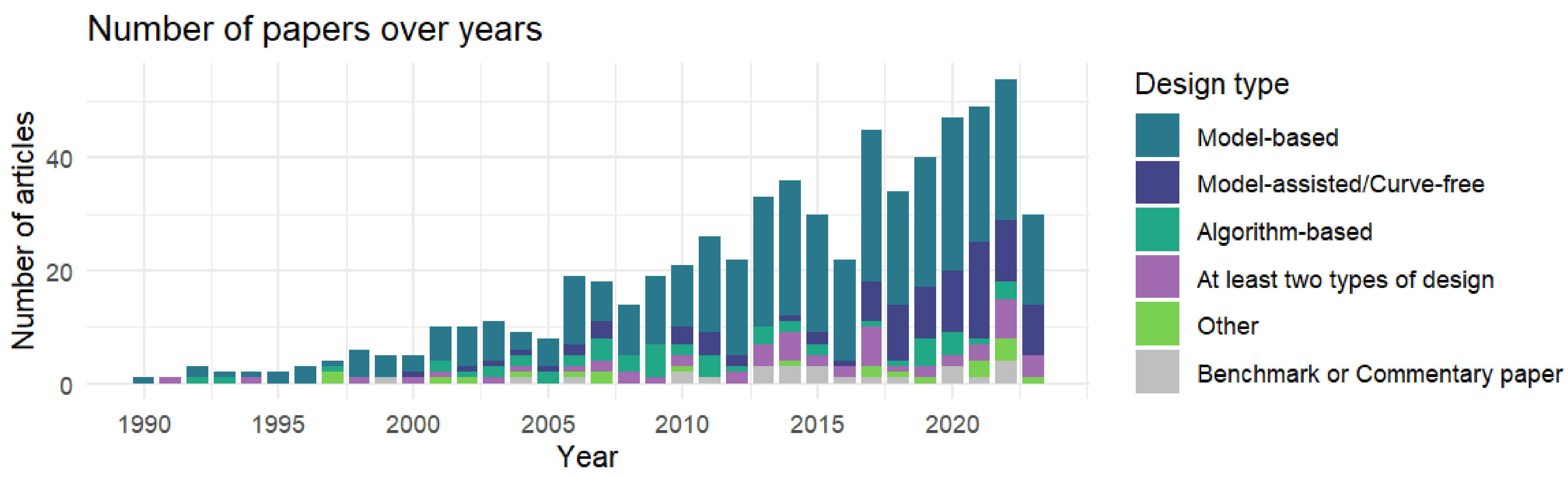
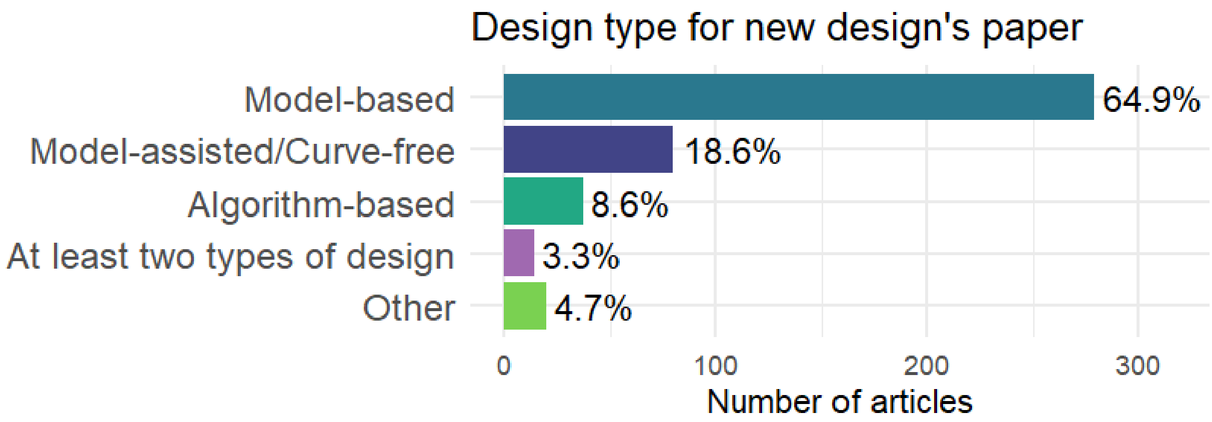
TYPE OF CONTRIBUTION



METHODOLOGY CONTRIBUTION OVER THE YEARS





Design types

- **Algorithm based designs:** 3+3, Group up-and-down designs
- **Model based designs: Continual Reassessment Method (CRM)**, BLRM
- **Model assisted designs:** mTPI, Keyboard, **BOIN**

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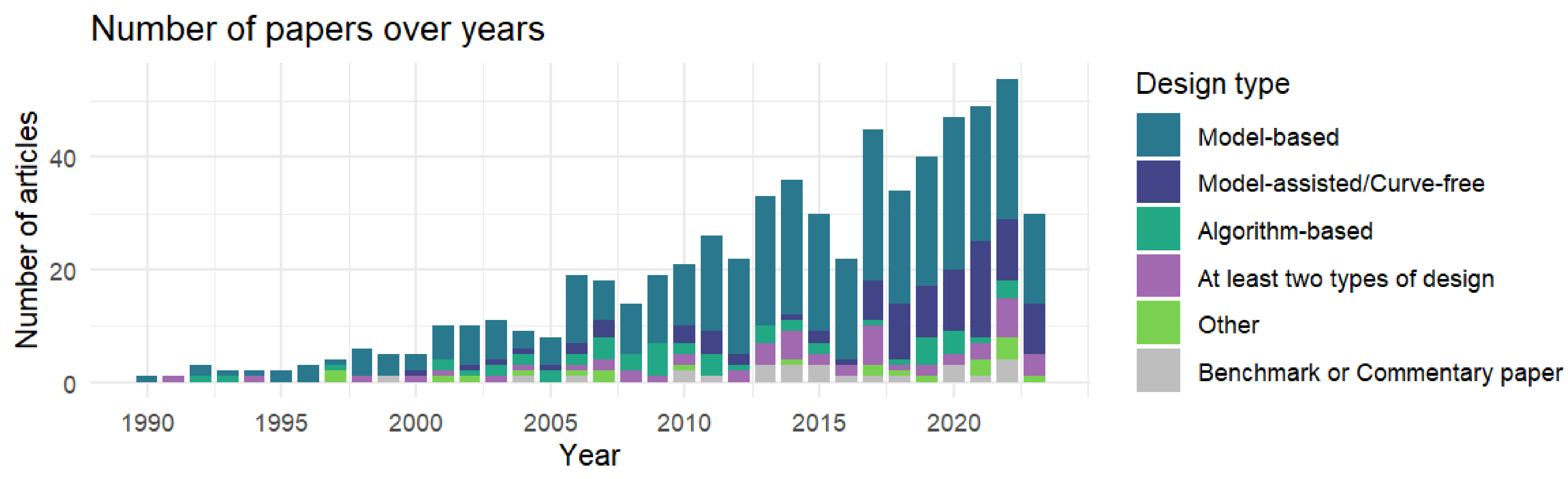
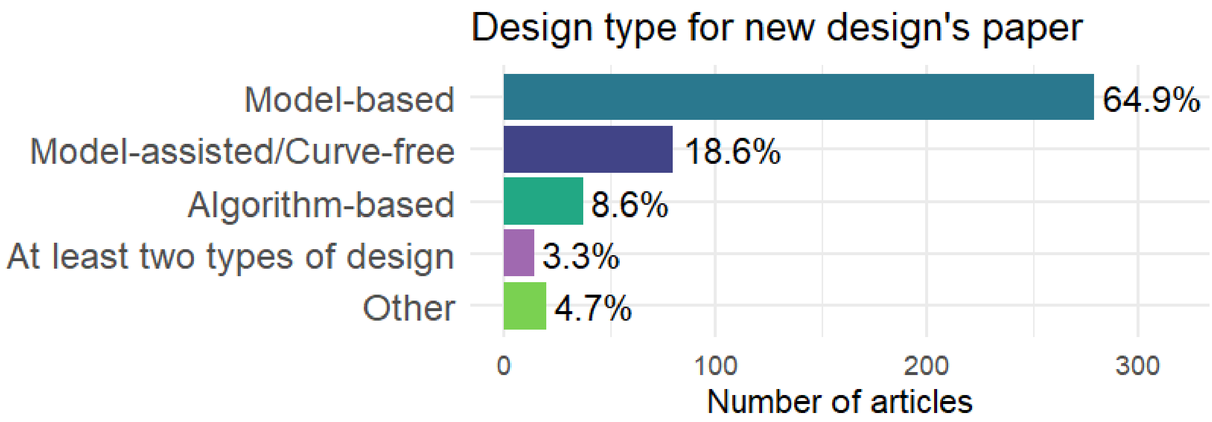
Methodology contribution over the years





eClinicalMedicine Part of THE LANCET *Discovery Science*

Assessing the reporting quality of early phase dose-finding trial protocols: a methodological review

Guillermo Villacampa [a], Dhrusti Patel [a], Haiyan Zheng [b], Jessica McAleese [a], Jan Rekowski [a], Olga Solovyeva [a], Zhulin Yin [a], Christina Yap [a,*]

Model-based and model-assisted designs identified in only 19% of Oncology dose-finding trial protocols posted on ClinicalTrials.gov in 2017-2023

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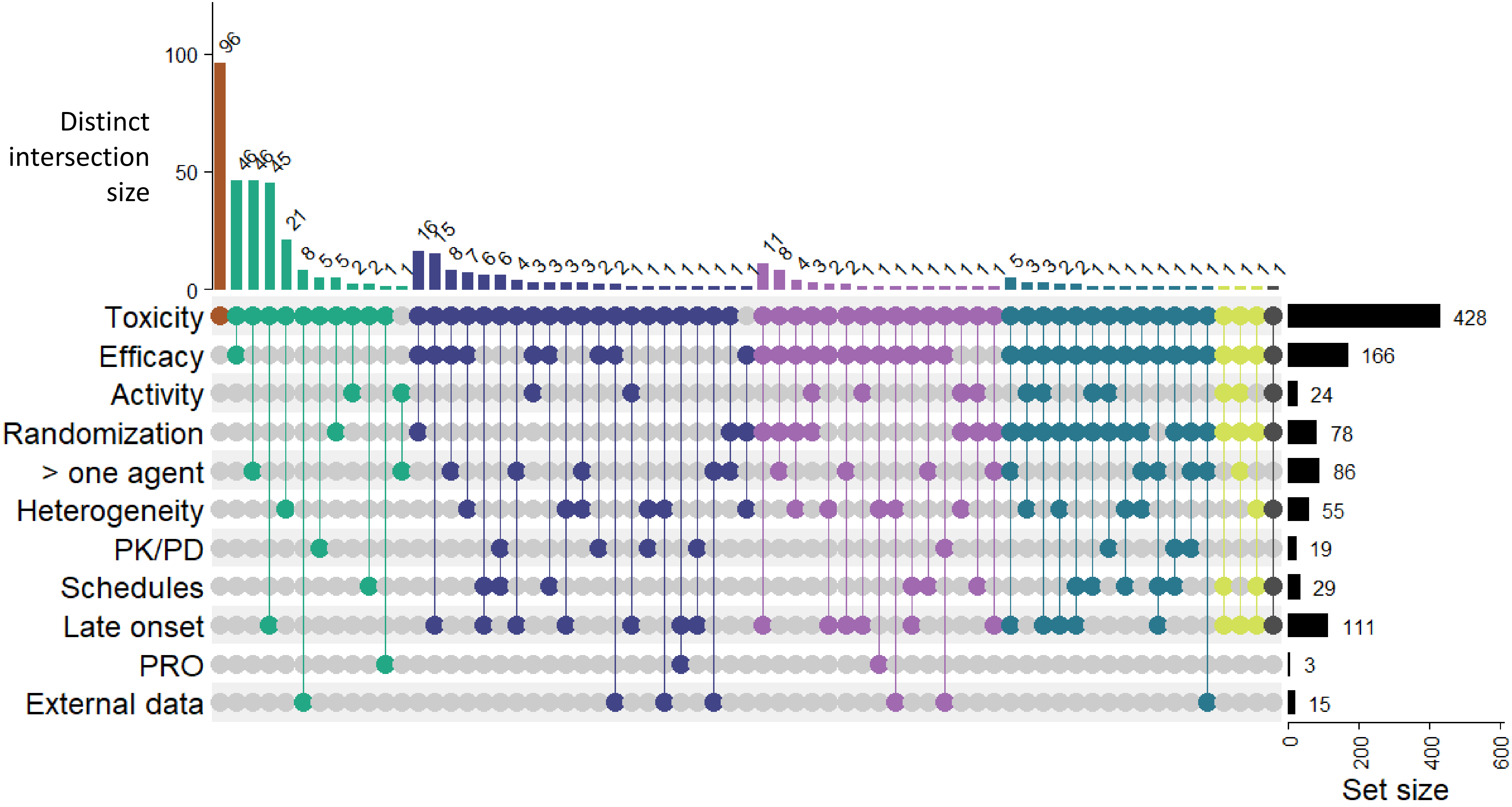
FEATURES COMBINATION FOR NEW DESIGNS PROPOSED



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TOXICITY/EFFICACY EVALUATION

166 out of 430 papers (39%) proposing new designs handle both toxicity and efficacy endpoints

DECISION CRITERIA

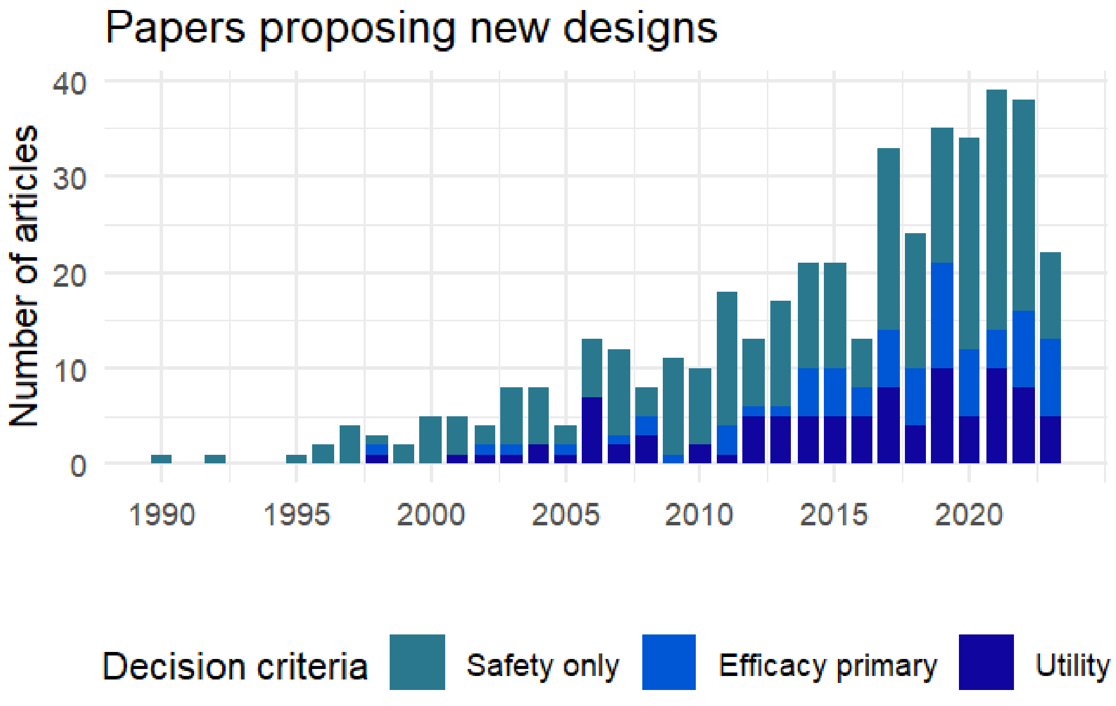
- **45%** of papers are based on **efficacy primary**

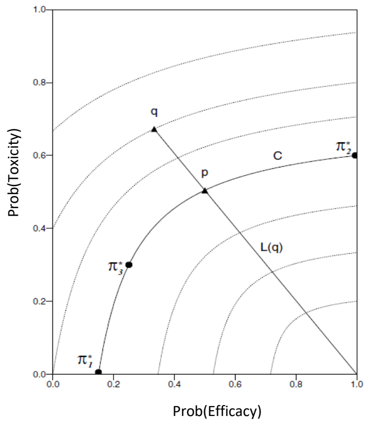
→ **Maximizes the probability of efficacy** among 'acceptable' doses in terms of safety

- **55%** of papers are based on **utility**

→ Identify the '**most desirable dose**' based on an efficacy–toxicity trade-off of desirability

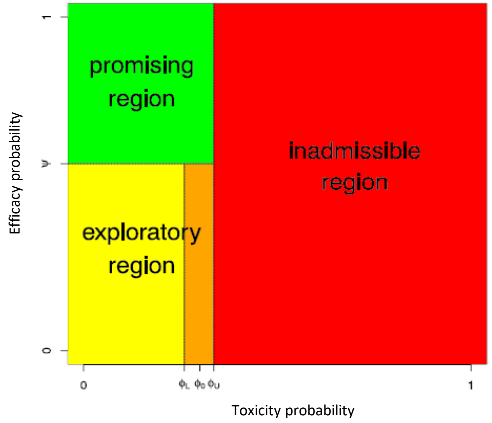
  - Efficacy/ toxicity contours
  - Utility function





Toxicity efficacy contour

Thall, P. & Cook. 2004



Toxicity and efficacy interval design

Lin, R. & Yin, G. 2017

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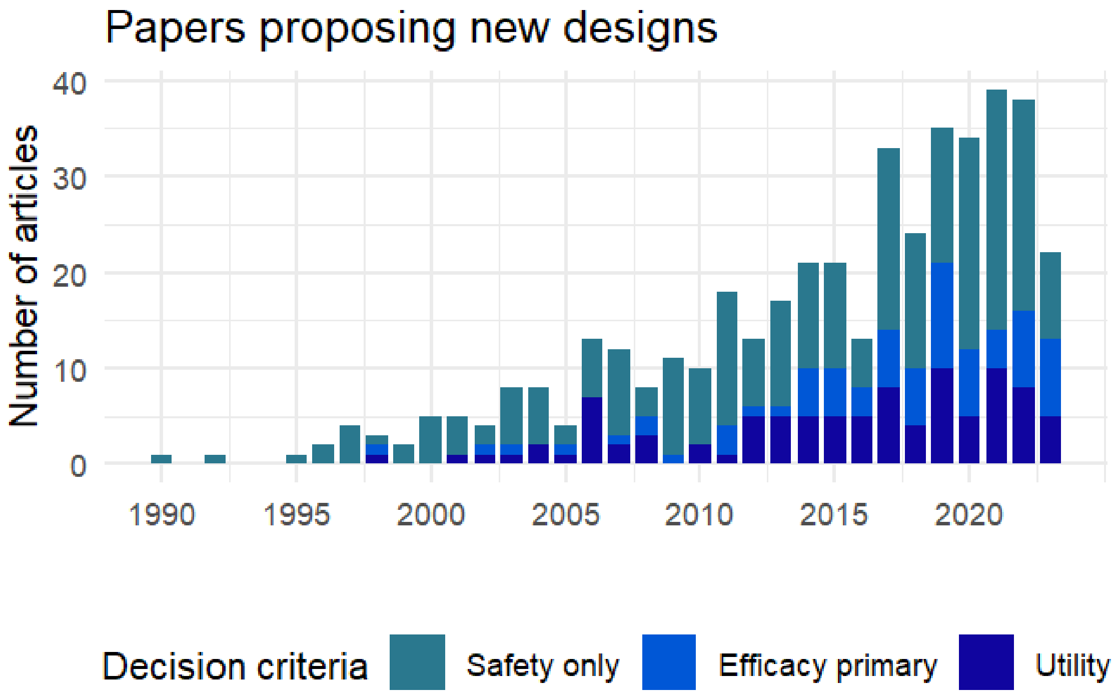
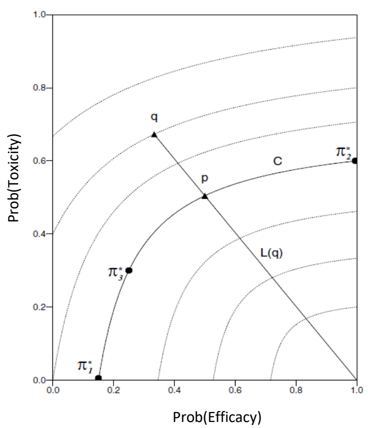
Challenges

- Long term assessment → use short-term endpoints for dose assignment, and long-term clinical endpoint to identify the optimal dose





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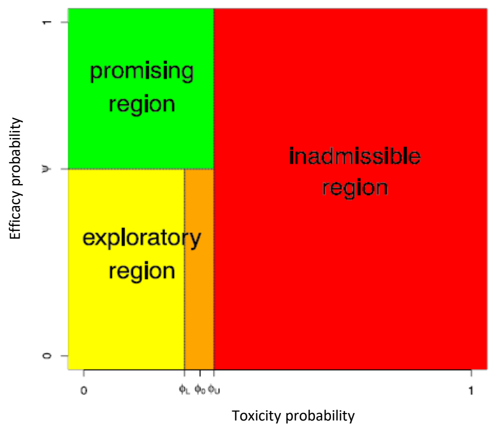

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Lin, R. & Yin, G. 2017

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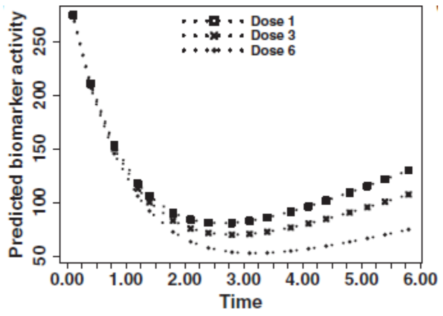
HETEROGENEITY

55 out of 430 papers (13%) proposing new designs

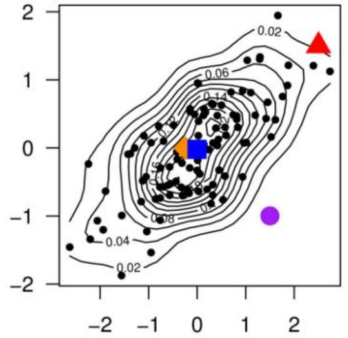
- **Biomarkers used as indicators of Activity**
  - Biomarkers produced by the tumor, reflecting the tumor evolution
  - Biomarkers reflecting the direct action of the treatment

- **Determining subgroup-specific optimal dose based on potential differences in**
  - tumor biology/ disease subtype
  - patient characteristics (biomarker expression at baseline or mid-treatment, age, sex, etc.)
  - treatment setting (previous or concurrent therapies)
  - ordered group (different susceptibility to toxicity)

Allowing inclusion of covariates, Bayesian information borrowing methods (hierarchical dose-response model), methods for **repeated biomarker measurements**



Altzerinakou, M-A & Paoletti, 2020



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PATIENT REPORTED OUTCOMES (PRO)

3 out of 430 papers (1%) proposing new designs

- Increased use of PRO in early phase trials, usually secondary endpoints
- PRO-CTCAE: different attributes for adverse events

- **VALIDATED INSTRUMENT FOR COLLECTING PATIENT REPORTED SYMPTOMS**

25. PRO-CTCAE™ Symptom Term: Skin dryness				
a. In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

Use of PROs:

- challenges related to the quality of the outcome
- and on how to gather the data

PRO-CTCAE https://healthcaredelivery.cancer.gov/pro-ctcae/

TOXICITY GRADES EVALUATION

18 out of 430 papers (4%) proposing new designs

- CTCAE toxicity grading

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Meaning	Mild	Moderate	Severe	Life-threatening	Death
Binary DLT	No DLT		**DLT**		

→ **Dose Limiting Toxicity - DLT** (0/1) may not be sufficient to fully characterize safety and tolerability of the drug, and **more comprehensive toxicity endpoints that account for low grade may be preferred**

Using richer toxicity data

- Ordinal toxicity outcome
- Score to summarize all adverse events
- Toxicity counts

Adverse event i	Severity j	Score
Fatigue	Grade 3	
Fever	Grade 1	$\sum w_{ij} X_{ij}$
Anemia	Grade 2	
Hypertension	Grade 1	

CTCAE V5.0 https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

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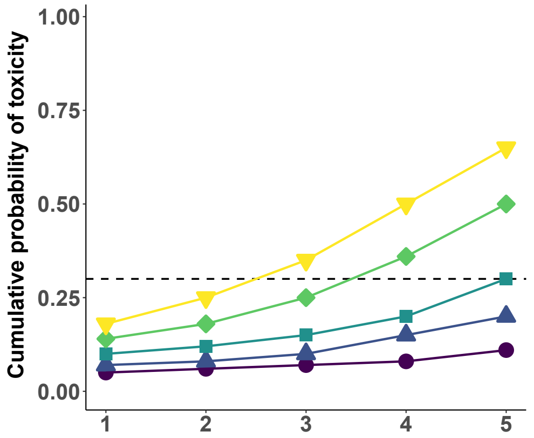
Late onset endpoints / Schedules evaluation

Cytotoxic agents : patients evaluated on a short period (1 cycle)
→ Patients may receive targeted therapies for much longer periods

- **Late onset endpoints : 99 out of 430 papers (23%) proposing new designs**
    - Late onset Toxicity only (60%)
    - Late onset Efficacy only (20%)
    - Both (20%)
- Conditional or cumulative probability of toxicity after **multiple cycles (32 out of 430 papers (7%) proposing new designs)**



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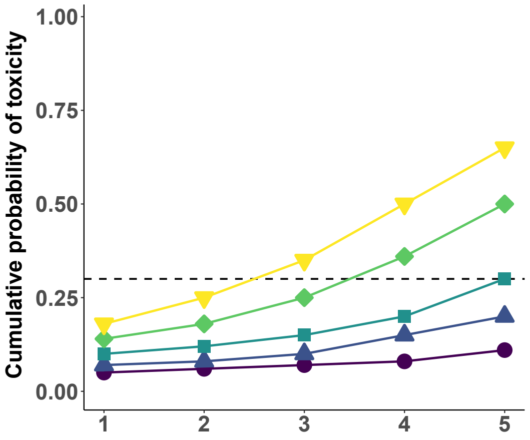
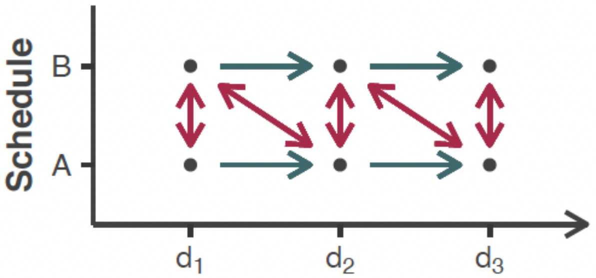


Optimal dosage : dose level + dosing regimen
Dose schedule (29 out of 430 papers (7%) proposing new designs)
Finding as a 2-dimensional problem (similarly to drug combinations)

- Ordering of schedules
  - **A**: days 1-3 $\prec$ **B**: days 1-6
  - **A**: days 1-3 & 8-10 $\prec$? **B**: days 1-6



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PHARMACOKINETIC PK(/PD) EVALUATION

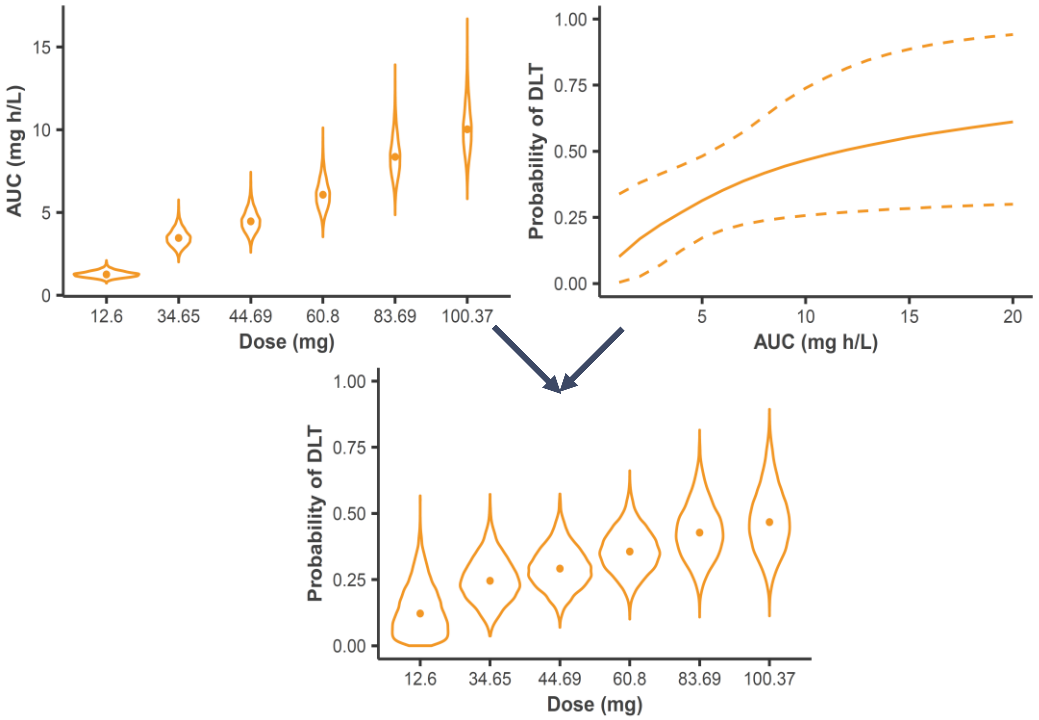
21 out of 430 papers (5%) proposing new designs

- **Need for a comprehensive analysis of the relationship of dose and exposure to both safety and efficacy**
- Designs developed incorporating pharmacokinetic (PK) data, using a measure of exposure (e.g AUC)

Challenges

- **not available after each cohort of patient**
- need of collaboration between pharmacometricians and statisticians

From Dose-DLT to (Dose-)Exposure-DLT



Micallef, S. et al. Cont clin trials com. 2022

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RANDOMIZATION

- **Compare multiple dosages in a randomized, parallel dose response trial**
  - **Comparability of patients receiving each dosage**, minimizing bias in estimation of dose- and exposure-response relationships
  - **Not powered**, assessment with a small sample size

73 papers of 430 papers (17%) proposing new designs

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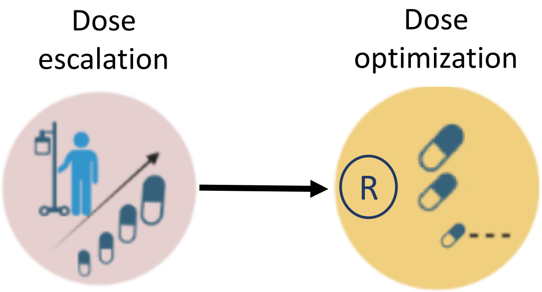
- **52% after escalation:** Dose optimization after the escalation phase in a **two-stage design** with (1) set of maximum tolerated dose selected and (2) (**adaptive**) **randomization** among acceptable / admissible doses



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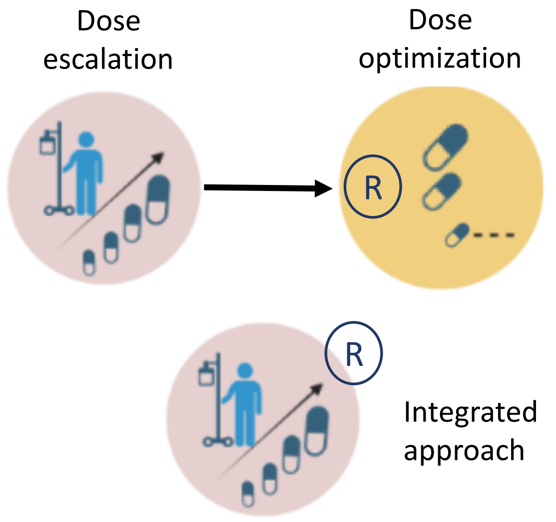
  - **5% both**



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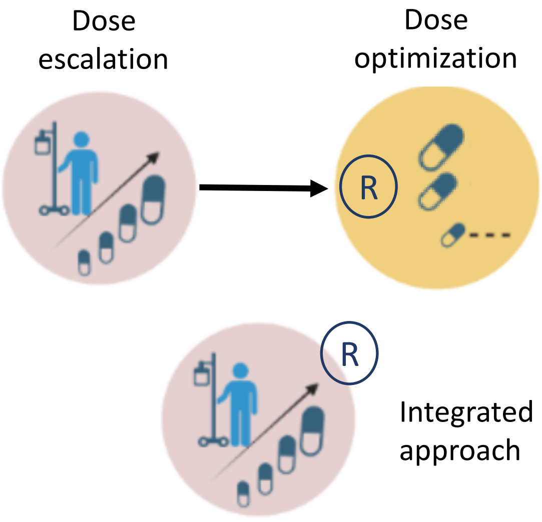
Challenges

- Adds complexity in terms of logistic
- Dose optimization requires comparing multiple doses based on the totality of data, and thus demands a larger sample size than MTD-finding trials



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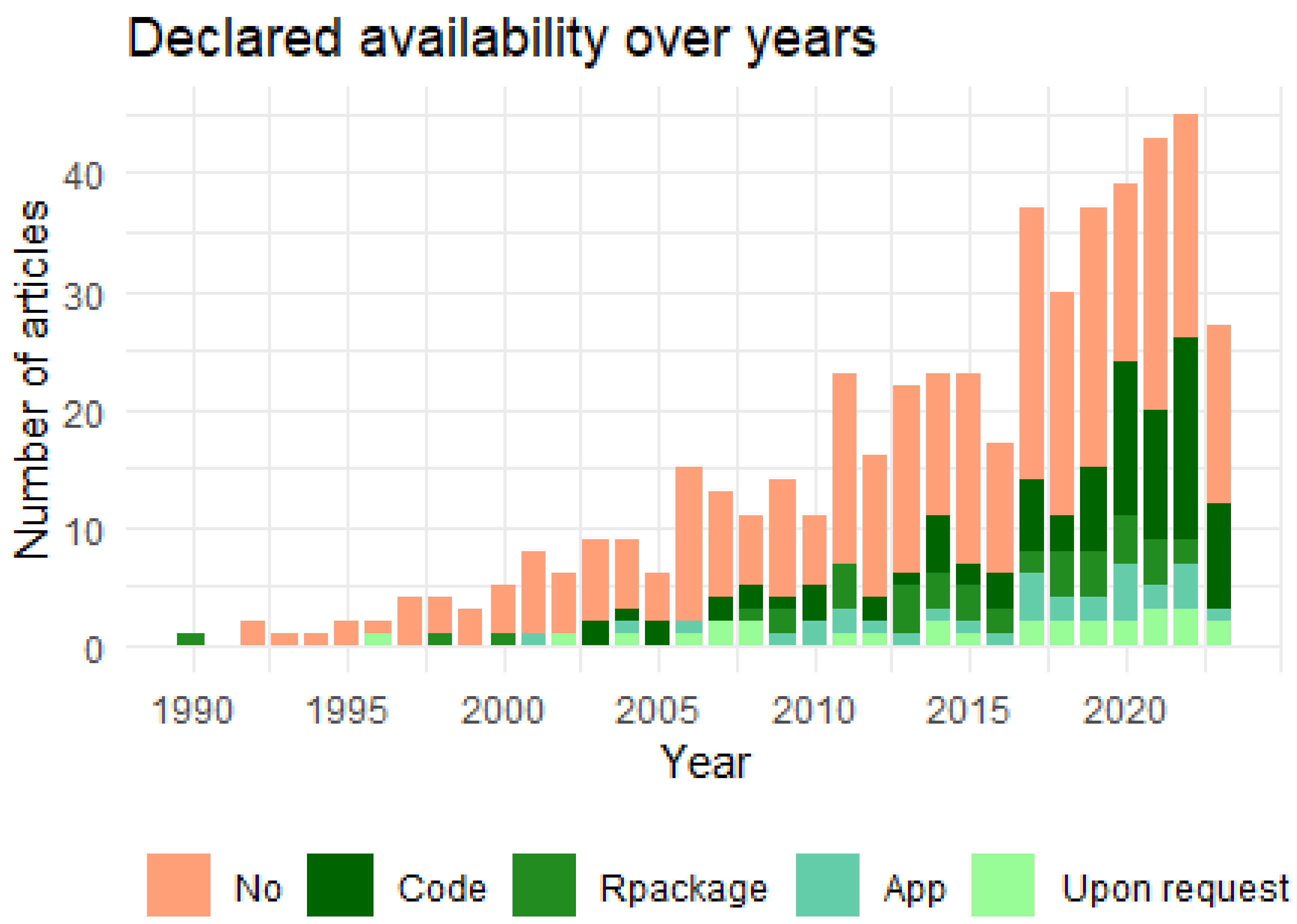
AVAILABILITY OF TOOLS

Availability for 196 out of 509 papers (39%) (New designs, Benchmark, Calibration, Programming tool papers)



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CONCLUDING REMARKS

- **Rich methodological literature exists on dose-finding in oncology**

→ Many Optimus-related topics have long been explored but remain underutilized in practice

→ Optimus project provides **new momentum for methodological application and innovation**

→ Encouraged efforts on **PROs** & trials including **dose optimization phases**

- **Importance of early discussions with FDA**
  - Before registrational trials & drug approval
  - Check regulatory agency requirements
  - Interdisciplinary interactions

- An update of this review in 2025 would be timely to assess whether a significant shift in the literature is observable, since the Optimus project was launched

- Manuscript will be submitted. The review database will be made accessible

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ANY QUESTIONS ?

PUBMED & SCOPUS SEARCH

Pubmed search:

((“dose finding”[Title/Abstract]) OR (“dose-finding”[Title/Abstract]) OR (“phase I”[Title/Abstract]) OR (“phase 1”[Title/Abstract]) OR (“phase I/II”[Title/Abstract]) OR (“phase I-II”[Title/Abstract]) OR (“phase 1/2”[Title/Abstract]) OR (“phase 1-2”[Title/Abstract]))

AND

((“maximum tolerated dose”[Title/Abstract]) OR (“cancer”[Title/Abstract]) OR (“oncology”[Title/Abstract]) OR (“toxicity”[Title/Abstract]) OR (“dose escalation”[Title/Abstract]) OR (“dose-escalation”[Title/Abstract]))

Scopus search:

(TITLE-ABS-KEY ("Phase 1") OR TITLE-ABS-KEY ("Phase I") OR TITLE-ABS-KEY ("Phase I-II") OR TITLE-ABS-KEY ("Phase I/II") OR TITLE-ABS-KEY ("Phase 1-2") OR TITLE-ABS-KEY ("Phase 1/2") OR TITLE-ABS-KEY ("Dose finding") OR TITLE-ABS-KEY ("Dose-finding")) AND (TITLE-ABS-KEY ("Oncology") OR TITLE-ABS-KEY ("Cancer") OR TITLE-ABS-KEY ("Maximum tolerated dose") OR TITLE-ABS-KEY("Toxicity") OR TITLE-ABS-KEY ("Dose escalation") OR TITLE-ABS-KEY ("Dose-escalation"))

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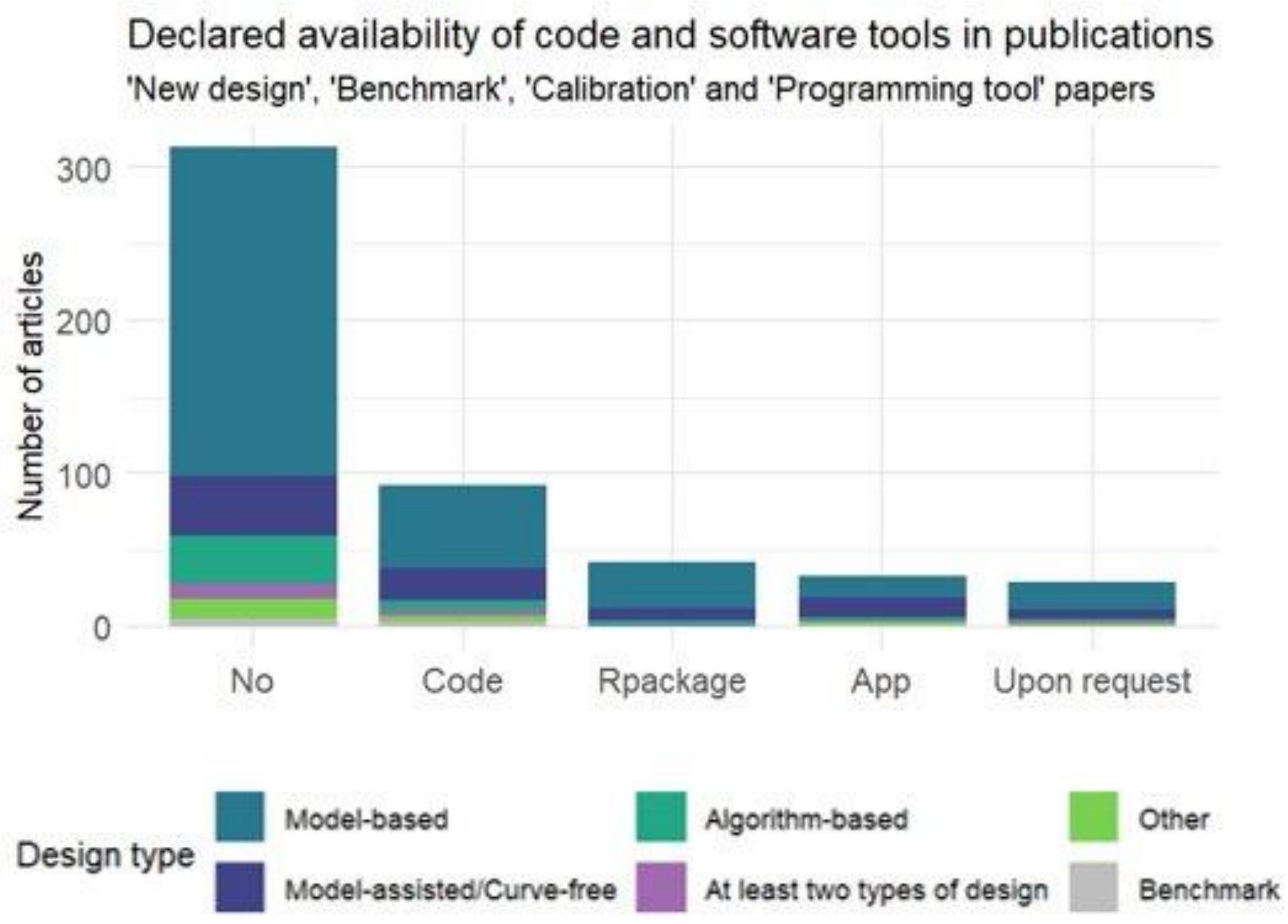
ADDITIONAL MEDICAL JOURNALS

PUBLISHING STATISTICAL METHODS ADDED TO THE LIST OF STATISTICAL JOURNALS

- BMC Medical Research Methodology
- Clinical Trials
- Computer Methods and Programs in Biomedicine
- Contemporary Clinical Trials
- Contemporary Clinical Trials Communications
- Controlled Clinical Trials

AVAILABILITY OF TOOLS



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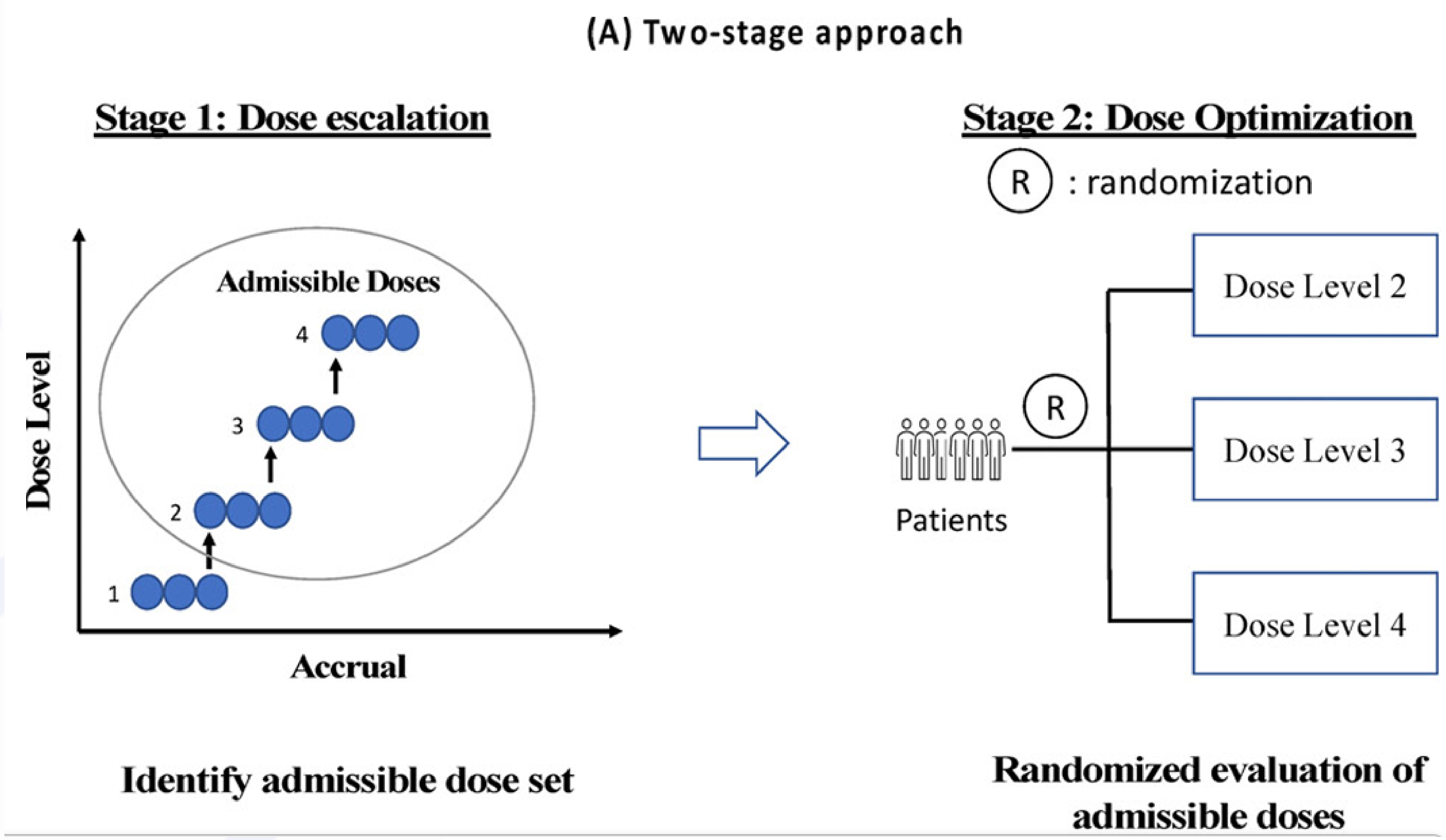
TWO-STAGE STRATEGY

- First stage is dose escalation based on toxicity or toxicity and efficacy to identify the admissible doses
- Second stage to randomize patients among the admissible doses



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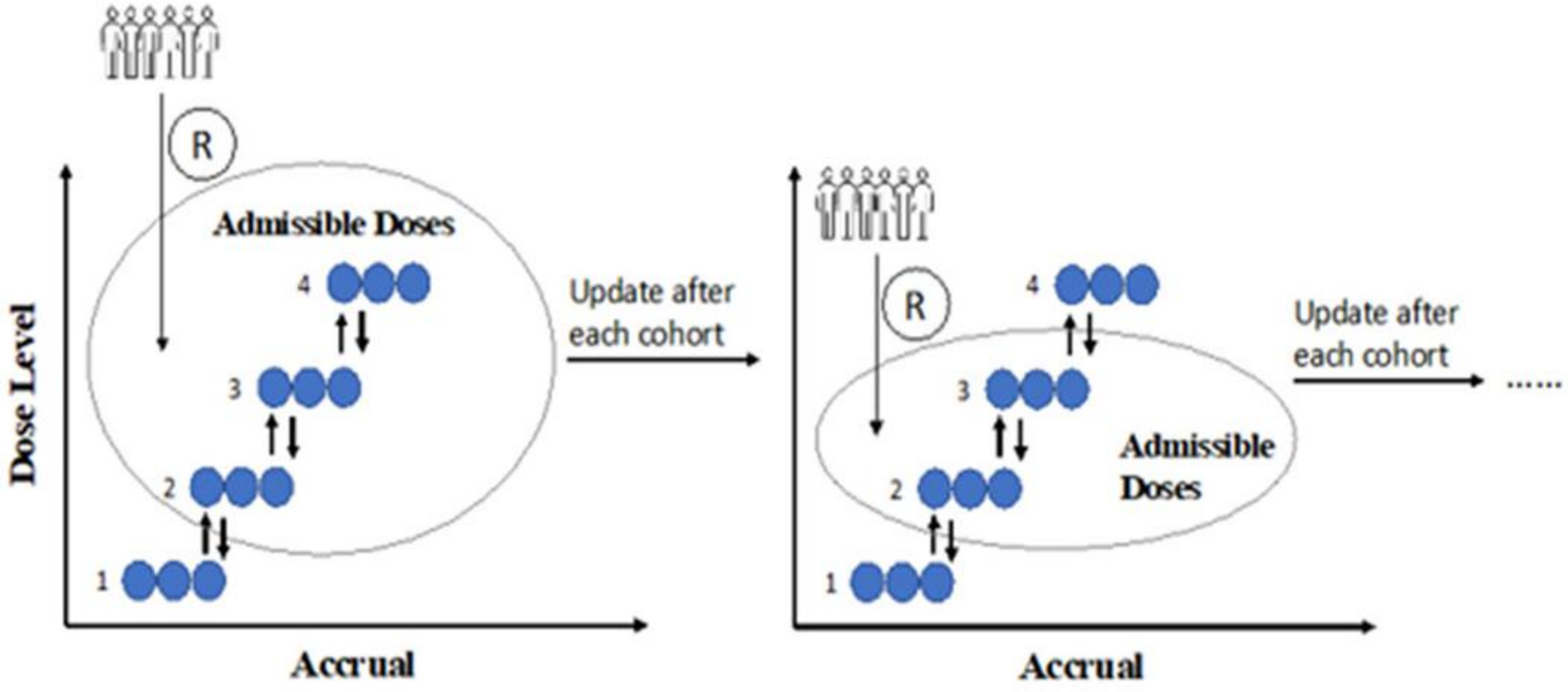
Statistics in Biopharmaceutical Research

Efficacy integrated approach

Admissible dose set is continuously updated after each cohort, and patients are assigned to admissible doses by adaptive randomization

(B) Efficacy-integrated approach



Continuous update admissible dose set for dose assignment

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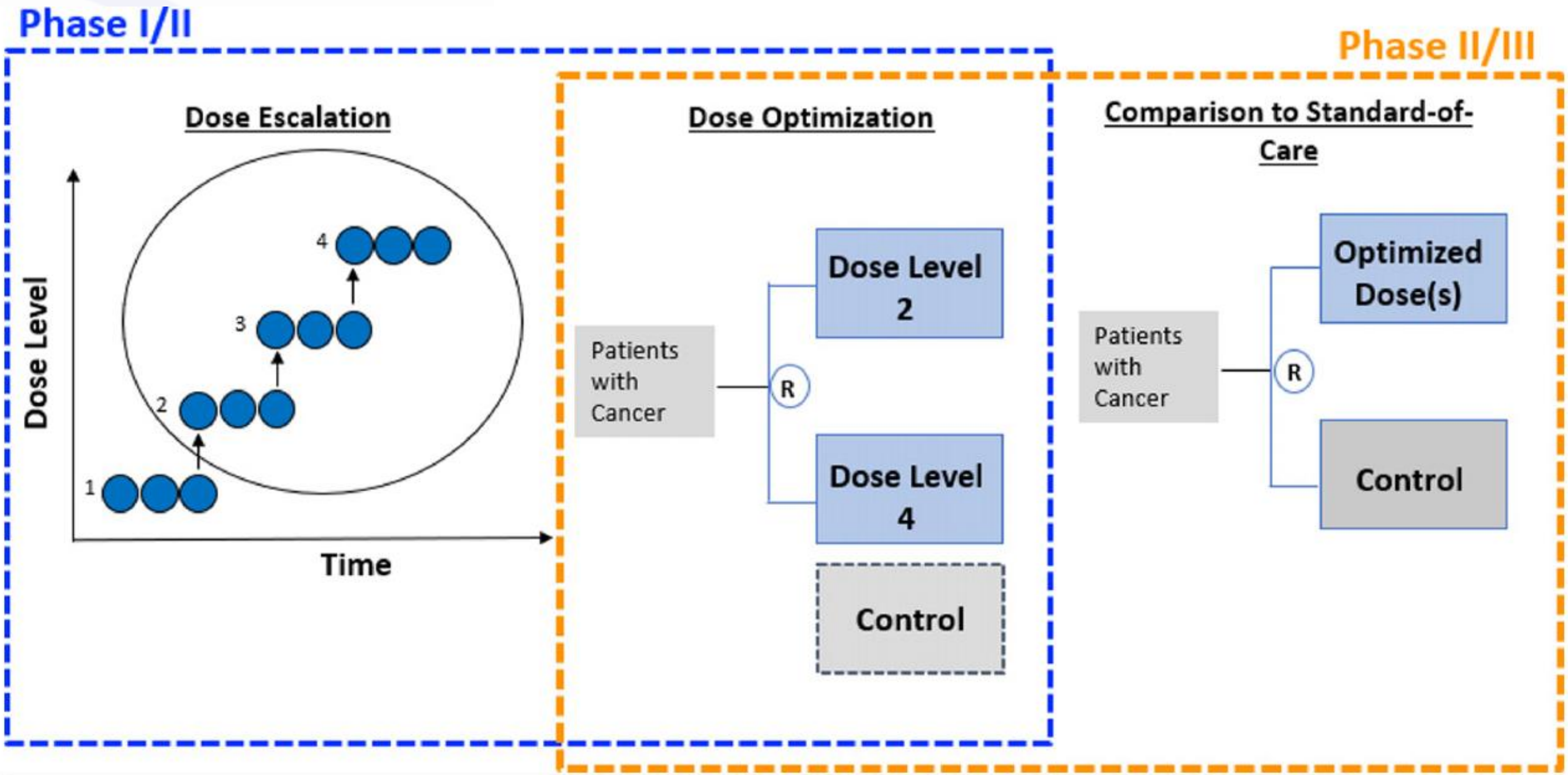
PHASE I/II AND PHASE II/III DESIGNS FOR DOSE OPTIMIZATION



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