ICR The Institute of Cancer Research

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Clinical Trials & Statistics Unit

Efficient

Flexible

Innovations in Early Phase Trials

Christina Yap

Professor of Clinical Trials Biostatistics

Group Leader, Early Phase and Adaptive Trials

Outline

1. Introduction to Adaptive Designs
2. Innovations in Early Phase Trial Designs
3. Conduct, Analysis & Reporting
4. Remarks

Adaptive Designs

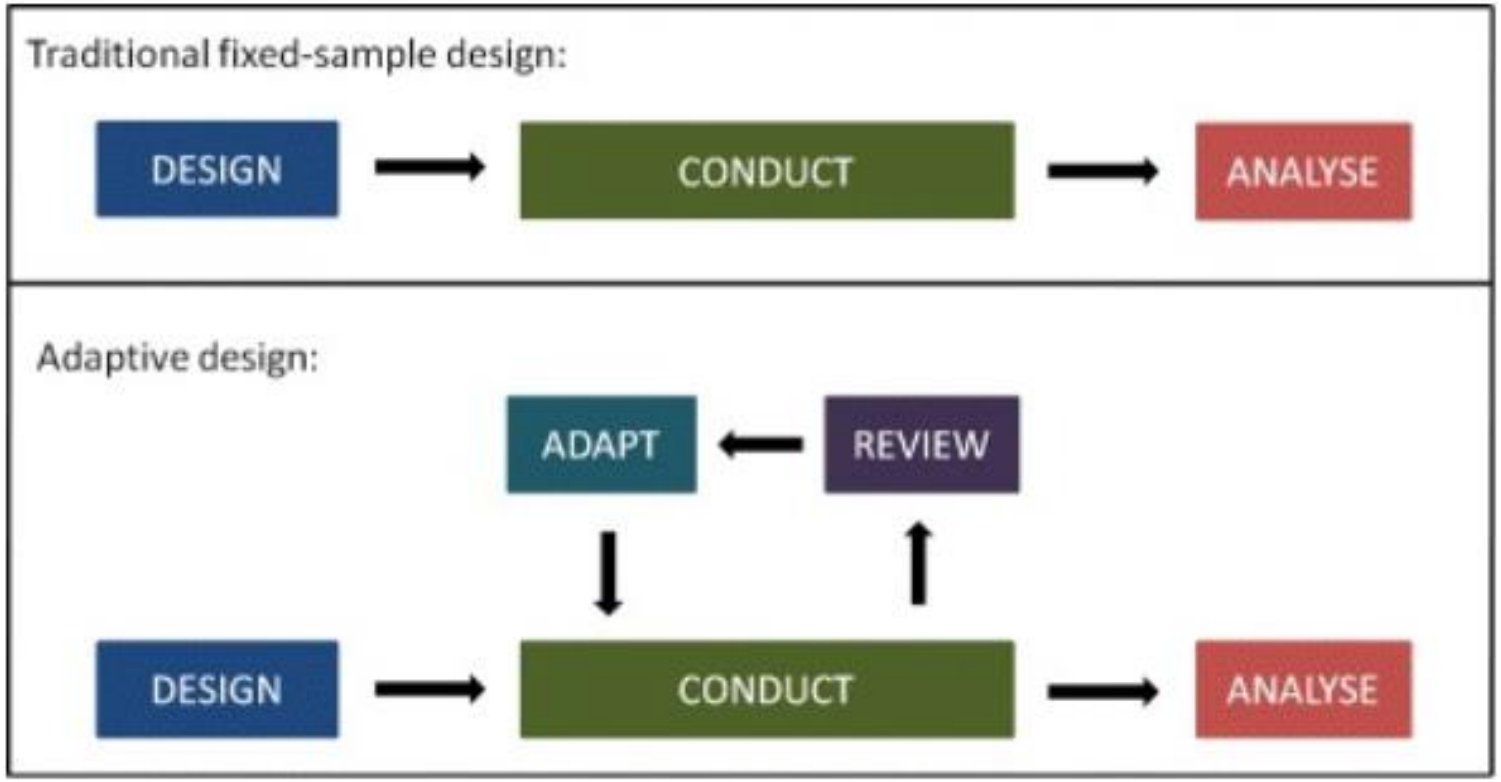
Pallmann *et al. BMC Medicine* (2018) 16:29
https://doi.org/10.1186/s12916-018-1017-7

BMC Medicine

CORRESPONDENCE Open Access

Adaptive designs in clinical trials: why use them, and how to run and report them

Philip Pallmann[1*], Alun W. Bedding[2], Babak Choodari-Oskooei[3], Munyaradzi Dimairo[4], Laura Flight[5], Lisa V. Hampson[1,6], Jane Holmes[7], Adrian P. Mander[8], Lang'o Odondi[7], Matthew R. Sydes[3], Sofía S. Villar[8], James M. S. Wason[8,9], Christopher J. Weir[10], Graham M. Wheeler[8,11], Christina Yap[12] and Thomas Jaki[1]



Schematic of a traditional clinical trial design with fixed sample size, and an adaptive design with pre-specified review(s) and adaptation(s)

Why use Adaptive Designs?

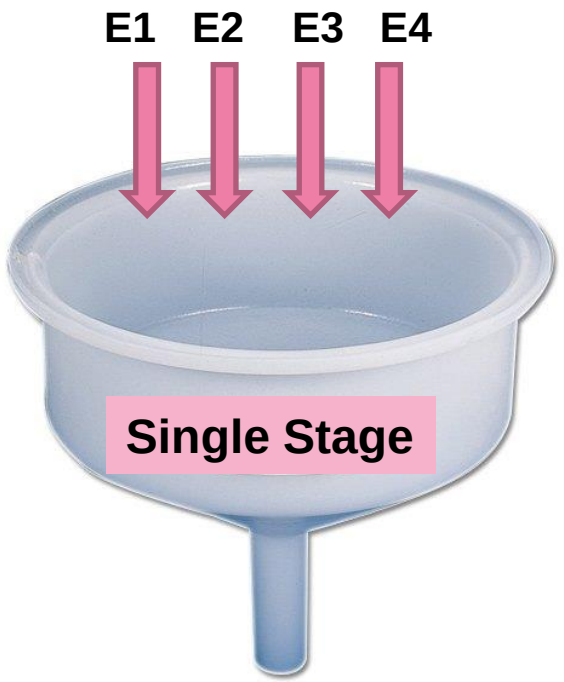
- ❑ Higher flexibility

Other benefits (depending on the adaptive features) can include:

- ❑ Higher accuracy
- ❑ Optimal allocation of patients
- ❑ Shorter trial duration
- ❑ Lower sample size

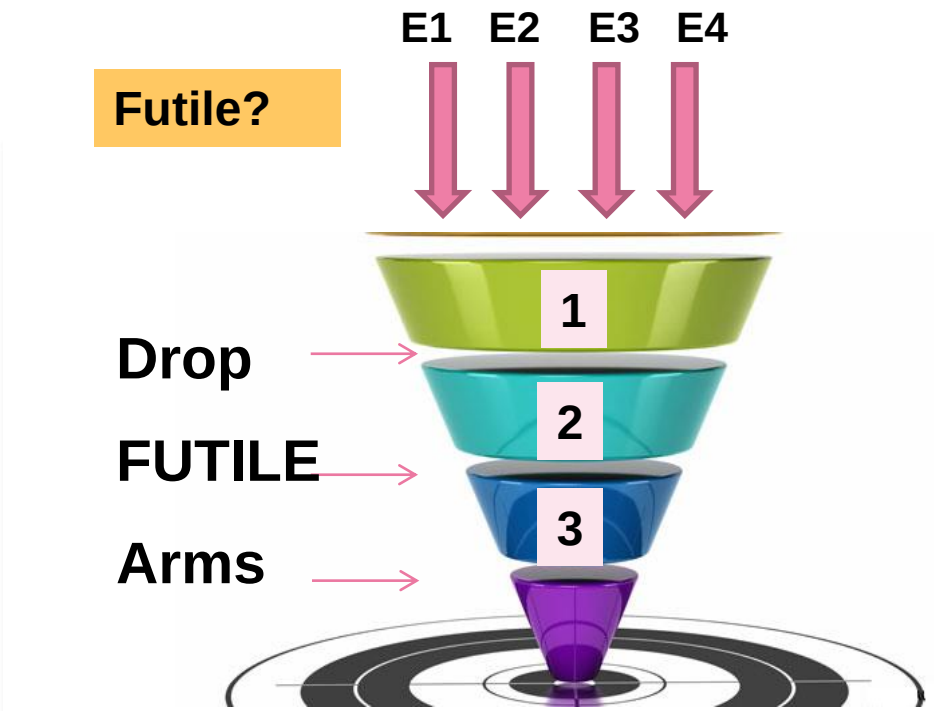
Design performance could be assessed by simulations.

Early Phase Randomised Selection Designs



Winner

(Simon et al 1985)

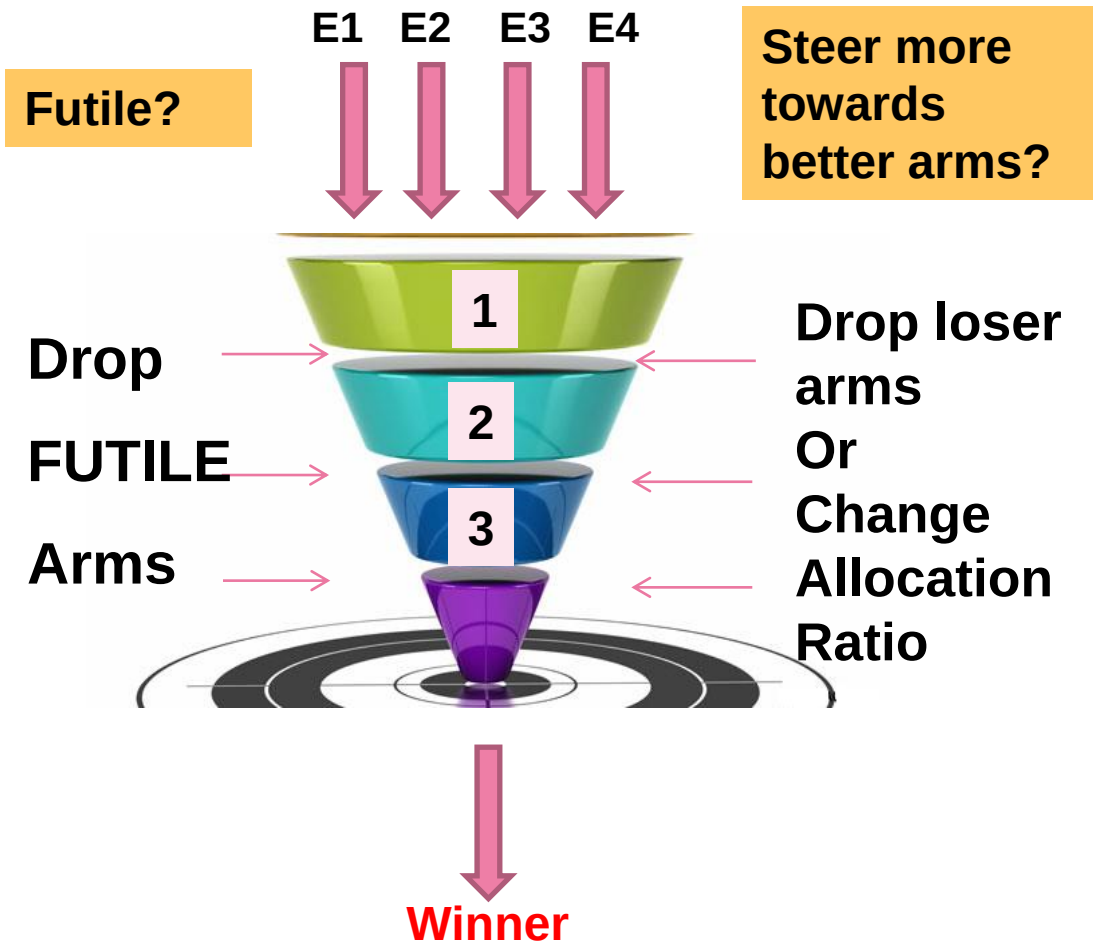


Adopted in Phase I/II ACE Trial [NCT03177187]

Winner

Simon, R., Wittes, R. E., Ellenberg, S. S. (1985). Randomized phase II linical trials. Cancer Treatment Reports 69(12), 1375–1381.

Early Phase Randomised Selection Designs



Thall, P. F., Wathen, J. K. (2007). Practical Bayesian adaptive randomisation in clinical trials. European Journal of Cancer 43(5), 859–866

Yap C and Cheung YK (2018). Sequential elimination in multi-arm multi-stage selection trials. Wiley StatsRef: Statistics Reference Online. https://doi.org/10.1002/9781118445112.stat08024

Yap, C., Lin, X., & Cheung, Y. K. K. (2015). Sequential Elimination in Multi-Arm Selection Trials. *Modern Adaptive Randomized Clinical Trials: Statistical and Practical Aspects*, *81*, 411-426, edited by Sverdlov, A (ed).

Classes of Phase I Trial Designs

Rule-based
(e.g., 3+3, Rolling 6)

- Simple - based on a pre-specified set of rules
- Inefficient/Inflexible - Decisions are based on DLT rate at current dose only.

Model-assisted
(e.g., BOIN, mTPI, Keyboard)

- Hybrid of the two – rules + statistical models.
- Efficient/Flexible - Decisions are based primarily at DLT rates at current dose; can target any DLT rate

Model-based
(e.g., CRM, TITE-CRM, EWOC, BLRM, EffTox)

- “Complex” – statistical model to model relationship between dose and outcomes (toxicity/activity)
- Efficient/Flexible - Decisions are based on DLT rates at ALL tested dose levels; can target any DLT rate.

Implementation of Advanced Designs in Oncology Trials

Model-assisted & Model-based Designs

5.4% (2009-2014)

8.6% (2014-2019)

19.0% (2017-2023)

Trial Results Publications

Trial Protocols


Articles

Dose-finding designs for trials of molecularly targeted agents and immunotherapies

Cody Chiuzan, Jonathan Shtaynberger, Gulam A. Manji, Jimmy K. Duong, Gary K. Schwartz, Anastasia Ivanova &

...show all

Pages 477-494 | Accepted author version posted online: 06 Feb 2017, Published online: 09 Mar 2017


ELSEVIER

European Journal of Cancer

Volume 158, November 2021, Pages 85-98

EJC

Review

Contemporary dose-escalation methods for early phase studies in the immunotherapeutics era

Daniel V. Araujo [a b 1], Marc Oliva [a c 1], Kecheng Li [d], Rouhi Fazelzad [e], Zhihui Amy Liu [d f], Lillian L. Siu [a]


eClinicalMedicine

Part of THE LANCET *Discovery Science*

Volume 60, June 2023, 102020

Articles

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]

JCO Precision Oncology > List of Issues > Volume 5 >

ORIGINAL REPORTS | Statistical Analysis

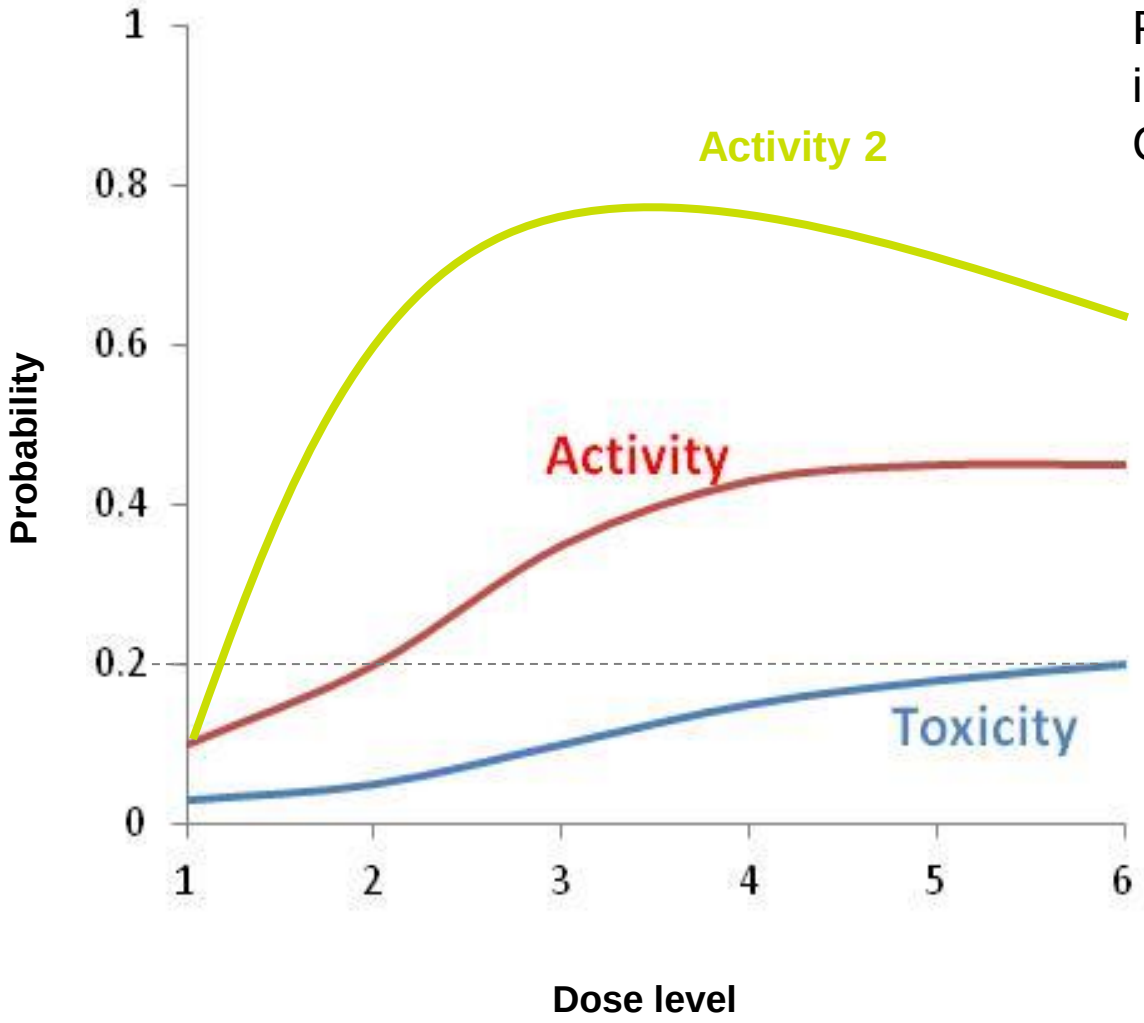
Would the Recommended Dose Have Been Different Using Novel Dose-Finding Designs? Comparing Dose-Finding Designs in Published Trials

Rebecca B. Silva, BA[1]; Christina Yap, PhD[2]; Richard Carvajal, MD[3]; and Shing M. Lee, PhD[1,3]

Model-based designs

- chose **dose levels higher** than the **published MTD** in 40% of the trials
- assigned **fewer patients** to **suboptimal doses**
- permitted **faster dose escalation**.

What if …. Activity does not increase with dose?



RP2D ≠ MTD

PK, PD,
immune-based biomarkers,
Clinical efficacy outcomes

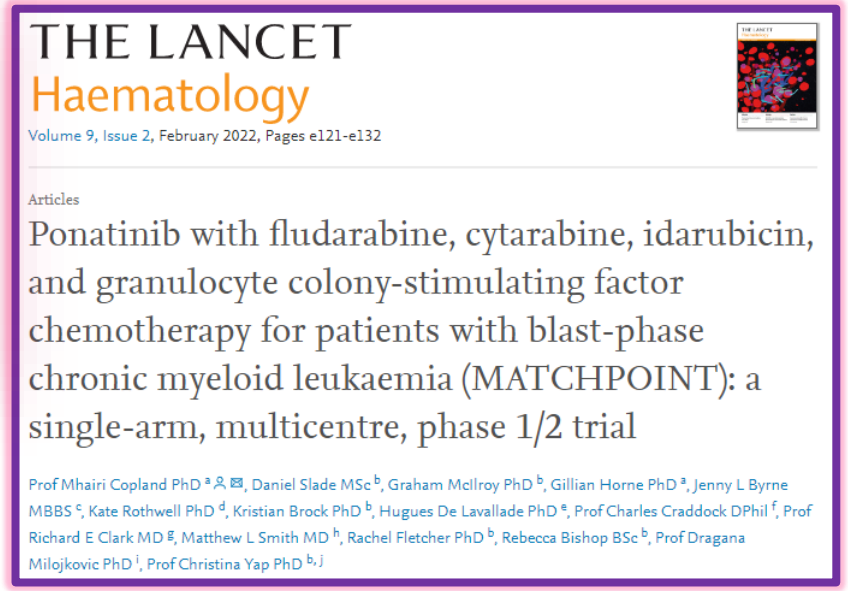
CASE STUDY: EFFTOX IN MATCHPOINT TRIAL

EffTox: A Bayesian design which **jointly models toxicity and activity** (response) and uses a efficacy-toxicity trade off criterion, to inform dose decisions

Thall and Cook 2004, “Dose-Finding based on Efficacy-Toxicity Trade-Offs”, Biometrics

Design Paper

Trial Results



EFFTOX IN MATCHPOINT TRIAL

Copland et al, Lancet Haem 2022

Patient Number	Activity	Toxicity (DLT)
1	No	No
2	No	Yes
3	Yes	Yes
4	Yes	No
5	No	No
6	No	No
7	Yes	No
8	Yes	No
9	Yes	No
10	Yes	No
11	Yes	Yes
13	No	Yes
14	Yes	No
15	Yes	No
16	Yes	No
17	Yes	No

- 4 dose levels; start at dose level 3.
- EffTox design recommended the **same dose (30mg)** throughout, taking into account both efficacy and toxicity outcomes.
- At recommended dose, posterior mean estimate of:
  - Activity: **68%**

    (95% credible interval 47–84%)
  - Toxicity: **25%**

    (95% credible interval 8–41%)

EFFTOX IN MATCHPOINT TRIAL

Copland et al, Lancet Haem 2022

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10	Yes	No
11	Yes	Yes
13	No	Yes
14	Yes	No
15	Yes	No
16	Yes	No
17	Yes	No

What would a 3+3 design have recommended?

2/3 DLTs at 30mg, de-escalate to 15mg

0/3 DLT at 15mg, stay at 15mg

0/3 DLT at 15mg.
A 3+3 design would have stopped with MTD declared at 15mg.

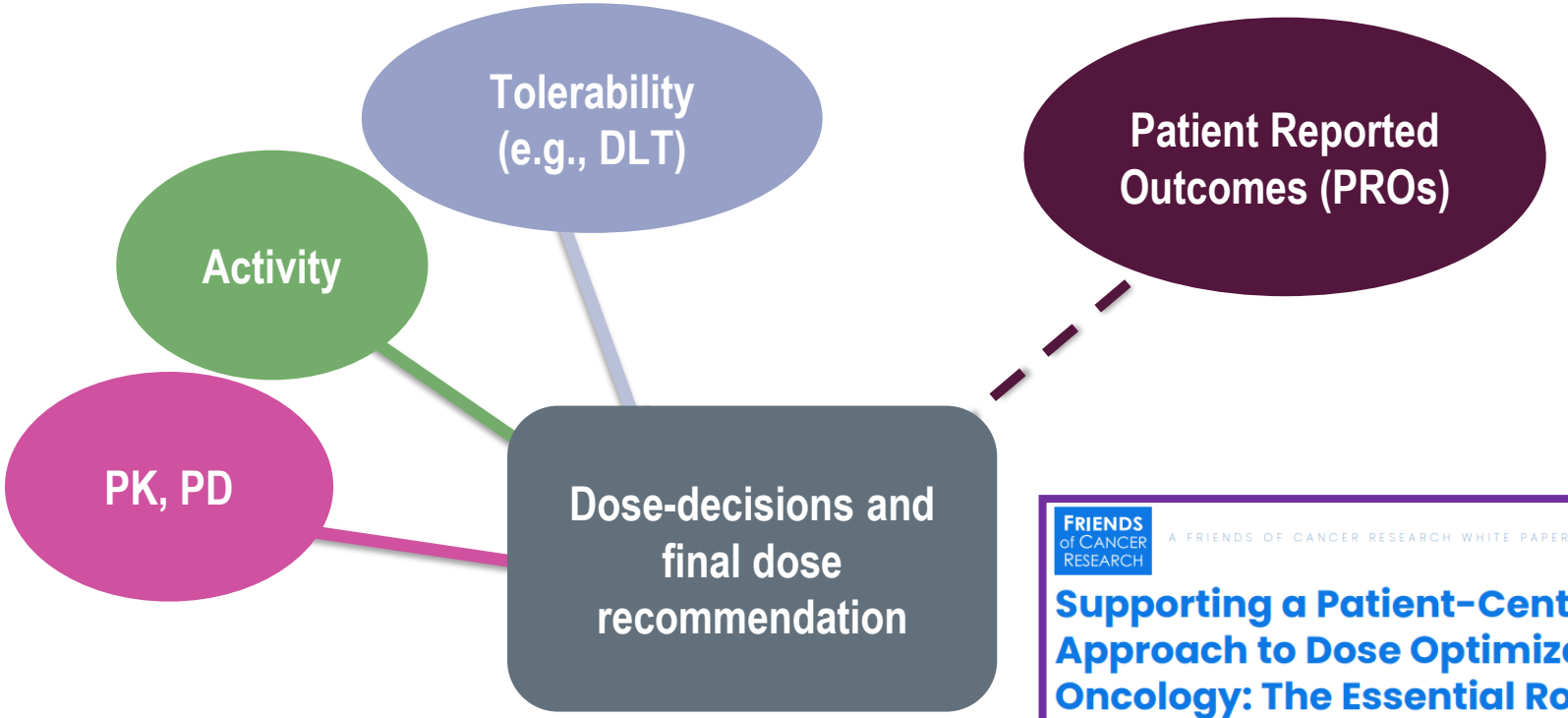
EffTox: recommended dose at 30mg

Incorporating other outcomes

Cancer Med. 2021 Nov;10(22):7943-7957. doi: 10.1002/cam4.4307. Epub 2021 Oct 22.

Trends in patient-reported outcome use in early phase dose-finding oncology trials – an analysis of ClinicalTrials.gov

Julia Lai-Kwon [1], Zhulin Yin [2], Anna Minchom [1], Christina Yap [2]



Only **5.3%** of trials had PRO endpoints

FRIENDS of CANCER RESEARCH — A FRIENDS OF CANCER RESEARCH WHITE PAPER

Supporting a Patient-Centric Approach to Dose Optimization in Oncology: The Essential Role of Patient-Reported Outcomes (PROs)

Friends of Cancer Research Annual Meeting 2022

Patient-Reported Outcomes for Tolerability Assessment in Phase I Cancer Clinical Trials FREE

Ethan Basch, MD ✉, Christina Yap, PhD

JNCI: Journal of the National Cancer Institute, Volume 113, Issue 8, August 2021, Pages 943–944, https://doi.org/10.1093/jnci/djab017

Conduct, Analysis and Reporting (All Designs)


RESEARCH METHODS AND REPORTING

BMJ 2022

Early phase clinical trials extension to guidelines for the content of statistical analysis plans

Victoria Homer,[1] Christina Yap,[2] Simon Bond,[3] Jane Holmes,[4] Deborah Stocken,[5] Katrina Walker,[5] Emily J Robinson,[6] Graham Wheeler,[7] Sarah Brown,[5] Samantha Hinsley,[8] Matthew Schipper,[9] Christopher J Weir,[10] Khadija Rantell,[11] Thomas Prior,[12] Ly-Mee Yu,[13] John Kirkpatrick,[14] Alun Bedding,[14] Carrol Gamble,[15] Piers Gaunt[1]

Trial Protocol → **Trial Analysis** → **Trial Reporting**

Parallel Group Randomised Trials

SPIRIT 2013
(Standard Protocol Items: Recommendations for Interventional Trials)

CONSORT 2010
(Consolidated Standards of Reporting Trials)

Conduct, Analysis and Reporting (All Designs)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Trial Protocol → **Trial Analysis** → **Trial Reporting**

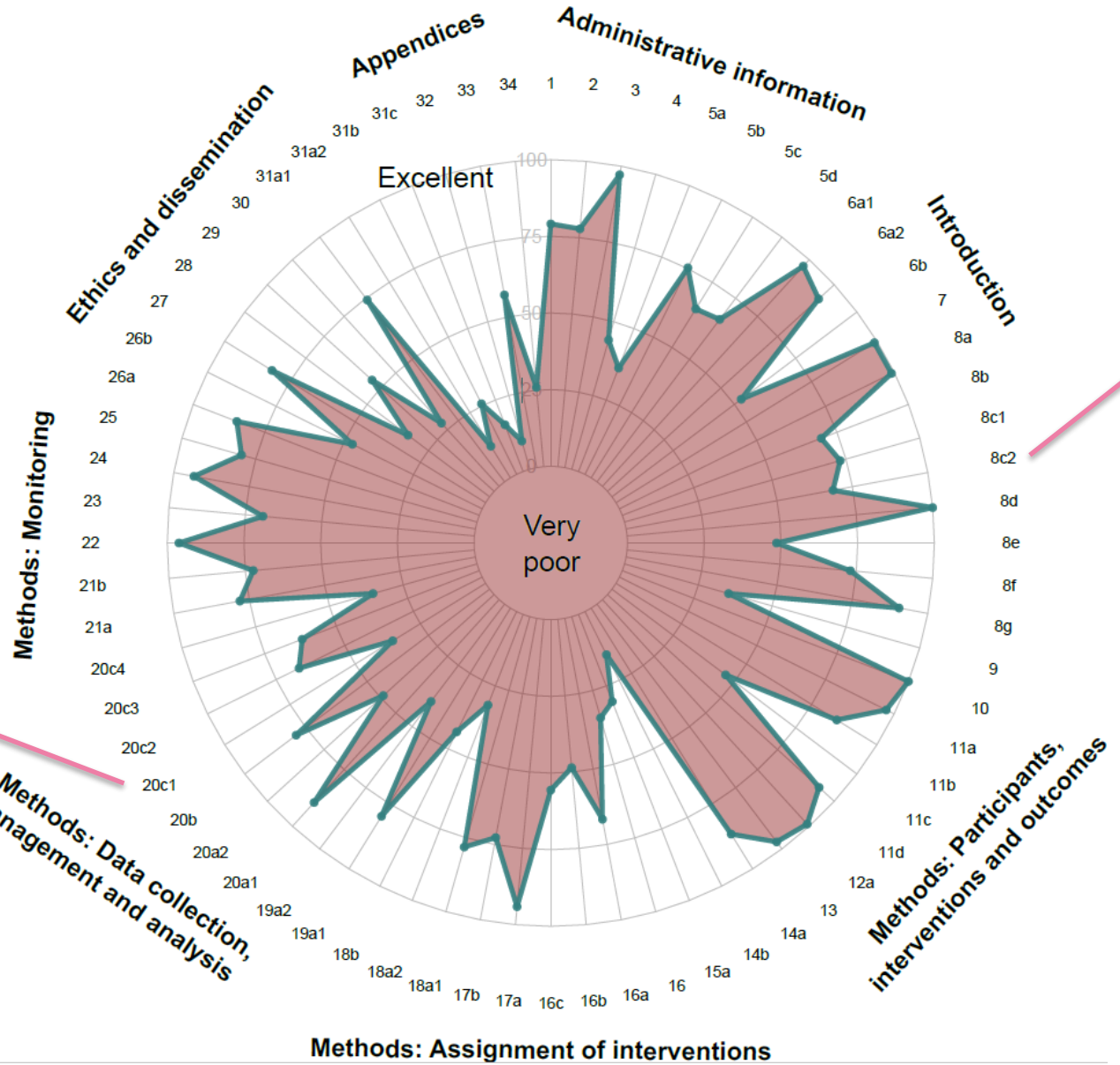
Guidance for Dose-finding Trials

?

?

Quality of Dose-finding Clinical Trial **Protocols**

Randomised selection of 106 protocols from 2017-2023 registered on ClinicalTrials.gov



Rationale for starting dose (69%)

Definition of dose-escalation analysis population (34%)

eClinicalMedicine

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Volume 60, June 2023, 102020

Articles

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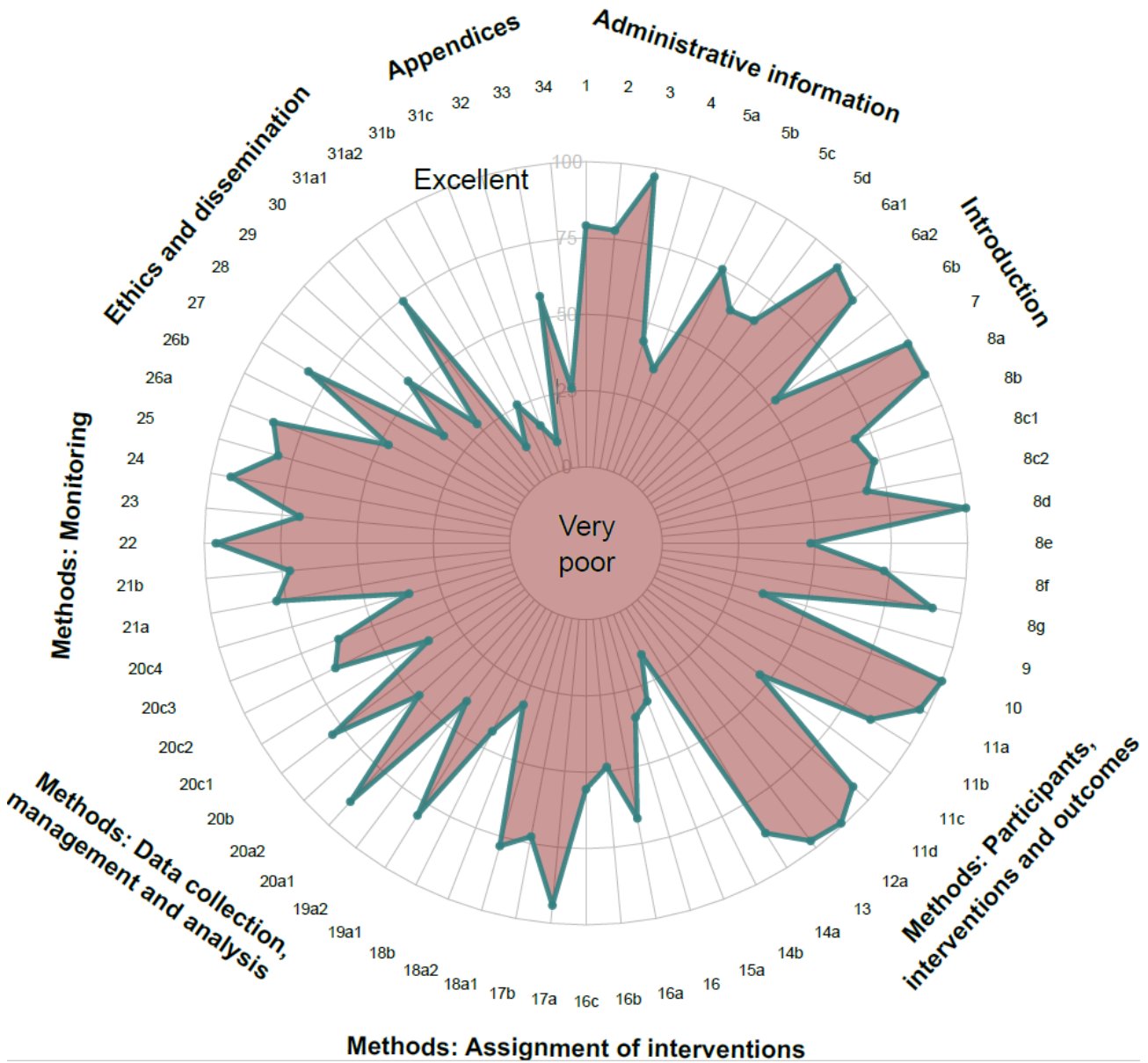

Inadequate reporting in trial protocols

and trial reports

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Reported Poorly ?

I can't find it!

OR

Adapted from https://tinyurl.com/mr46t77k

"To allow accurate assessment of early phase trial results, it is crucial they are reported precisely, transparently and in sufficient detail."

nature medicine

Yap et al 2022

Clear need for **international consensus-driven guidelines** to recommend **essential items** that should be presented in dose-finding trial protocols and reports, to promote **greater clarity**, **reproducibility**, **informativeness** and **utility of results**.

→ **DEFINE (Dose-finding Extension) Project**

https://www.icr.ac.uk/DEFINEstudy

Conduct, Analysis and Reporting (All Designs)

International consensus-driven guidance


RESEARCH METHODS AND REPORTING

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Research article | Open Access | Published: 05 July 2023

Development of consensus-driven SPIRIT and CONSORT extensions for early phase dose-finding trials: the DEFINE study

Olga Solovyeva, Munyaradzi Dimairo, Christopher J. Weir, Siew Wan Hee, Aude Espinasse, Moreno Ursino, Dhrusti Patel, Andrew Kightley, Sarah Hughes, Thomas Jaki, Adrian Mander, Thomas R. Jeffry Evans, Shing Lee, Sally Hopewell, Khadija Rerhou Rantell, An-Wen Chan, Alun Bedding, Richard Stephens, Dawn Richards, Lesley Roberts, John Kirkpatrick, Johann de Bono & Christina Yap

BMC Medicine **21**, Article number: 246 (2023) | Cite this article

Trial Protocol

Trial Analysis

Trial Reporting

Lay Summary

SPIRIT-DEFINE

(Standard Protocol Items: Recommendations for Interventional Trials – Dose-finding Extension)

The BMJ, in press

CONSORT-DEFINE

(Consolidated Standards of Reporting Trials – Dose-finding Extension)

The BMJ, in press

BMC Medicine 2023

With thanks to the DEFINE guidelines co-authors

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Deborah Ashby, Imperial College London, St Mary's Hospital, UK;

And 206 multidisciplinary Delphi survey participants from 24 countries

Comments

- The **opportunities** afforded by innovative trial designs are **enormous**.
- Such designs (including basket, umbrella, platform trials) are **infrequently implemented** but are **expected to increase** due to focus on genomic medicine and to do **smarter** and **quicker** trials
- Innovative design elements can help ensure that **maximum information** is obtained from the research effort.
- Undoubtedly, it requires **increased resources, specialist expertise, planning and coordination,** but the **gain in efficiencies** can last for many years.
- **Need** for **further methodology development** and evidence of effective implementation

Comments (cont..)

Effective reporting is **NOT OPTIONAL** –

it is a **FUNDAMENTAL** aspect of

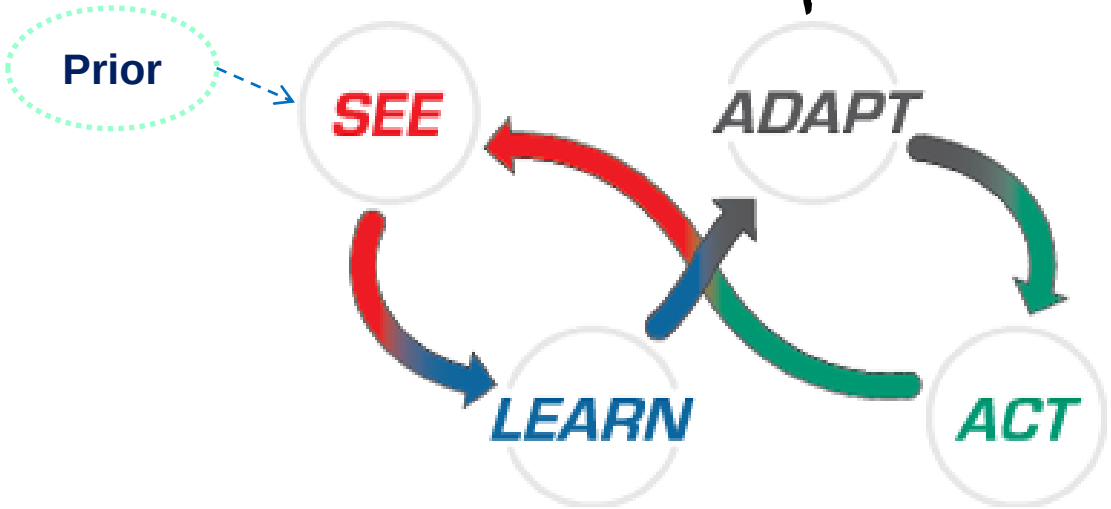
conducting **high-quality research**

"To maximise the benefit to society, you need to not just do research, but do it well".

Doug Altman (1948-2018), statistician, pioneer, luminary.

Acknowledgements:
- MATCHPOINT Trials Team
- Funders: Bloodwise (Trials Acceleration Programme) and MRC/NIHR
- Patients and Family

Thank You



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