December 2nd, 2022

Statistical and logistical issues of platform trials - summary introduction -

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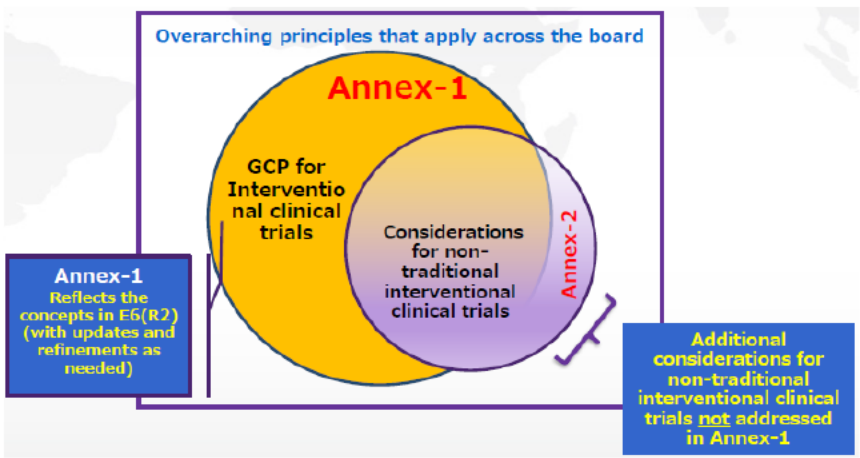
Modernization of clinical trial design

U.S. : 21st century cures act（2016～）

- The aim is to reduce costs for drug/device development.
- The ideas include ***complex innovative designs (CIDs)***
  - **efficient use of real-world data/evidence**
  - **master protocol (basket / umbrella / platform trials)**
  - **adaptive designs**

ICH : ICH-E6(R3), E8(R1), E11A

- Discussions are ongoing to **efficiently use evidence/data from non-traditional clinical trials**.



http://atdd-frm.umin.jp/2017/slide/2-3.pdf
https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/21stCenturyCuresAct/default.htm
https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf

Master protocol

***One overarching protocol* designed to answer multiple questions:**

- **Multiple treatments**
- **Multiple diseases**
- **Multiple subgroups (e.g., defined by biomarkers)**

Three types of master protocol

- **Umbrella trial**: multiple enriched sub-trials for one disease
- **Basket trial**: one treatment for multiple diseases with specific biomarker status
- **Platform trial**: sub-trials continually enter and exit

Number of platform trials

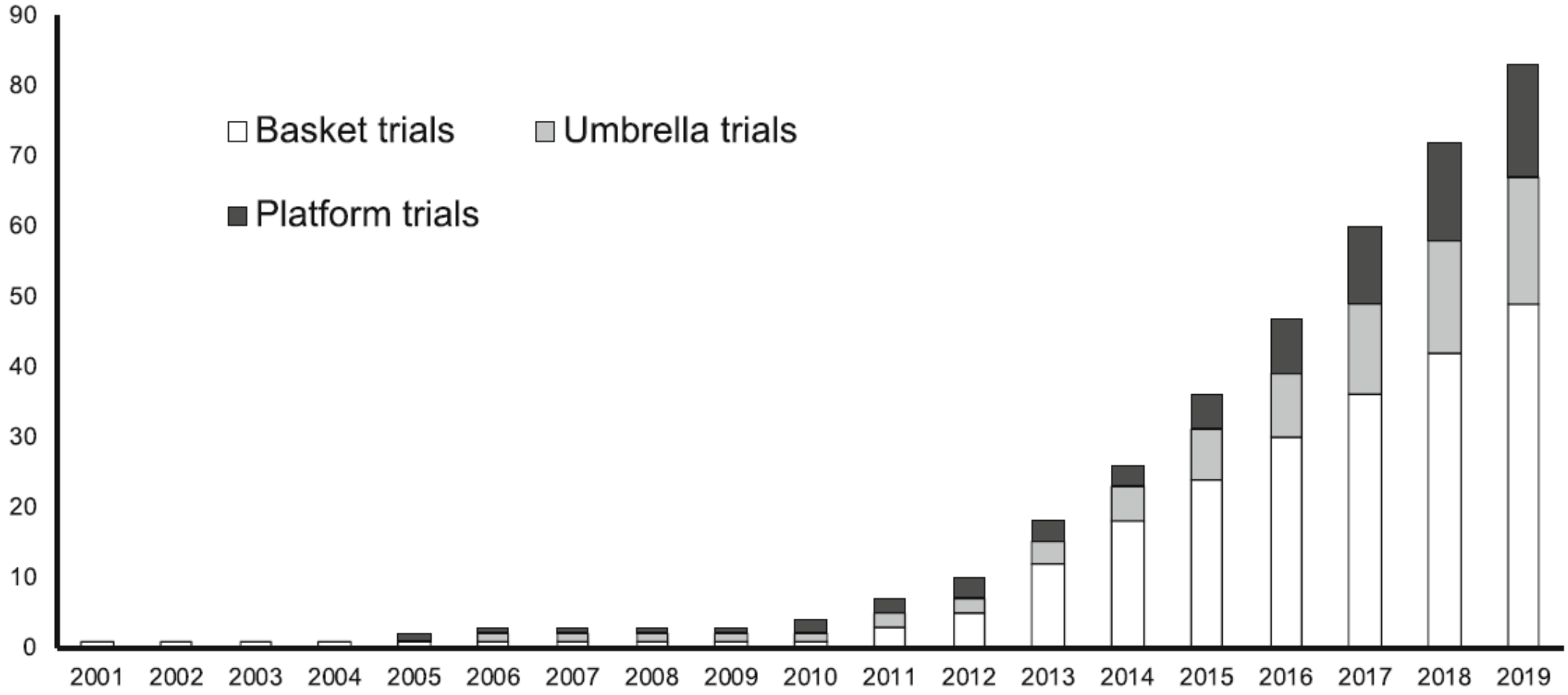


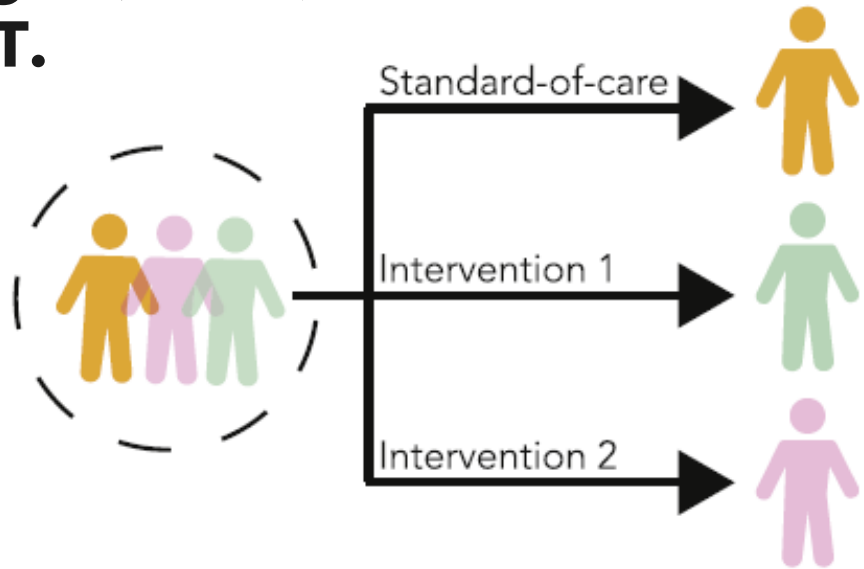
Fig. 2 Trends of master protocols over time. This figure illustrates the accumulating number of basket (white), umbrella (gray), and platform (black) trials over time. The clip art in the figure was generated by the authors

Why are platform trials needed?

Sometimes, there is urgent medical needs for developing multiple experimental candidate treatments at the same time.

- Infectious diseases (rescue treatments for Ebola disease, Covid-19, and so on)
- Oncology (e.g., neoadjuvant chemotherapies for high-risk breast cancer patients)

Platform trial applies *shared-controlled designs (SCDs)* which can assess multiple experimental groups in a single RCT.



Existing platform trials (selected)

Table 1 | **Design features of select funded adaptive platform trials**

Feature	I-SPY 2	REMAP-CAP	GBM AGILE	INSIGhT[13]	EPAD	DIAN	Precision Promise	PREPARE FLU
Registration number	NCT01042379	NCT02735707	NCT03970447; Alexander et al.[42]	NCT02977780	Ritchie et al.[45]	NCT01760005	NA[a]	ISRCTN27908921
Population	Breast cancer	Severe pneumonia	Glioblastoma	Glioblastoma	Alzheimer disease	Alzheimer disease	Pancreatic cancer	Influenza
Phase	II	IV	II/III	II	II	III	II/III	IV
Proportion of experimental agents	14/16	0/9[b]	1/2	3/4	3/3	3/3	NA[a]	NA
Time of primary outcome	6 months	3 months	TTE	TTE	4 years	>4 years	TTE	1 week
Patient selection								
Subtype stratification	Y	Y	Y	Y	Y	N	Y	N
Study arms								
Multiple arms	Y	Y	Y	Y	Y	Y	Y	Y
Multiple domains	N	Y	N	N	N	N	N	N
Common control	Y	Y	Y	Y	Y	Y	Y	Y

SCDs versus 2-armed RCTs

Multiplicity adjustments due to multiple control-test comparisons:

- 2-armed RCTs: not needed
- SCDs
  - inferentially dependent (e.g., various dose levels of the same drug) → needed;
  - inferentially independent → adjustments may not be needed.

SCDs can be a more efficient approach than multiple 2-armed RCTs.

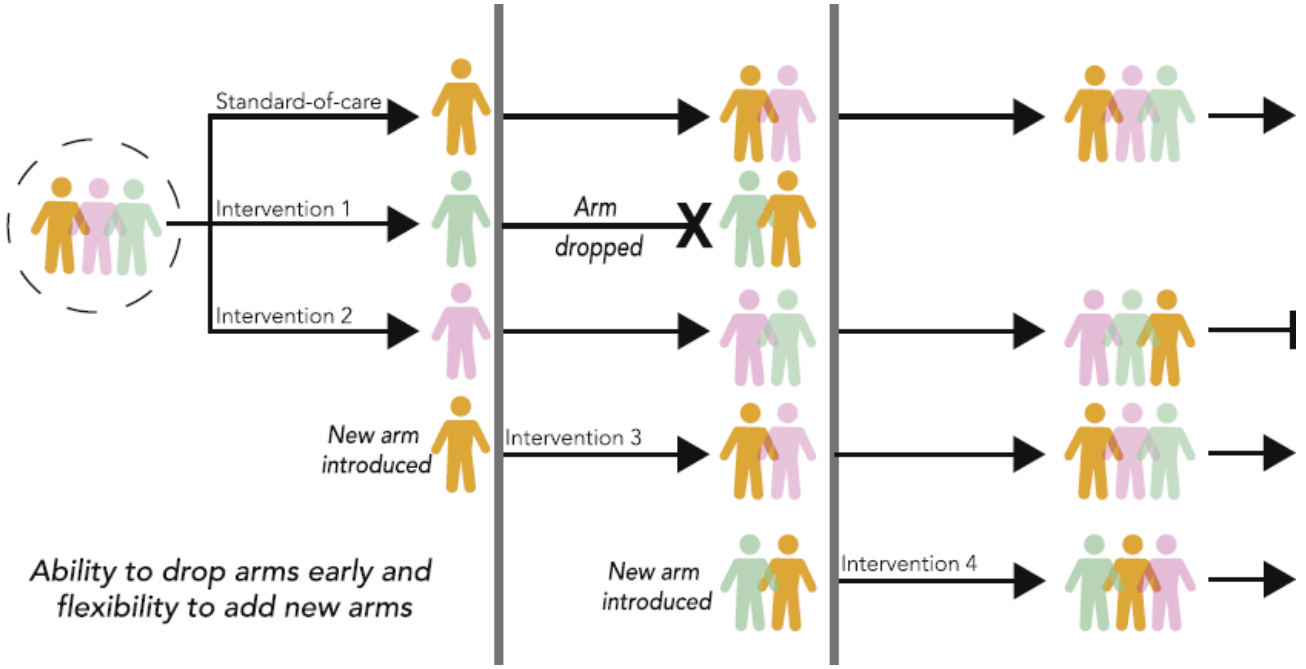
- #patients in the control arm in SCDs is smaller than that in multiple 2-armed RCTs.
- Power of SCDs can be higher than that of multiple 2-armed RCTs
  even with multiplicity adjustments (Drs. Uemura and Lori will explain later).

Plausible *adaptive* features in SCDs

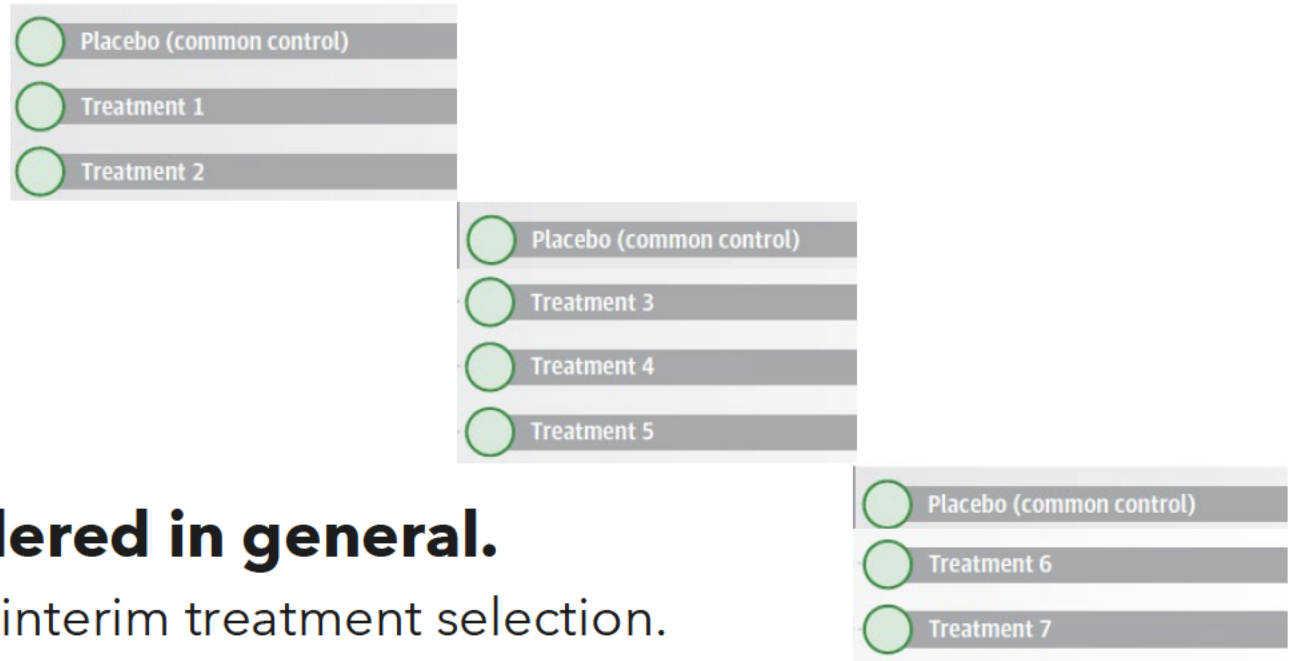
A trial would be more efficient and/or ethical if …

(1) New arm introduction is allowed.

(2) Dropping existing arm(s) due to futility or efficacy.



Closed platform trials



Consecutive conduct of SCDs

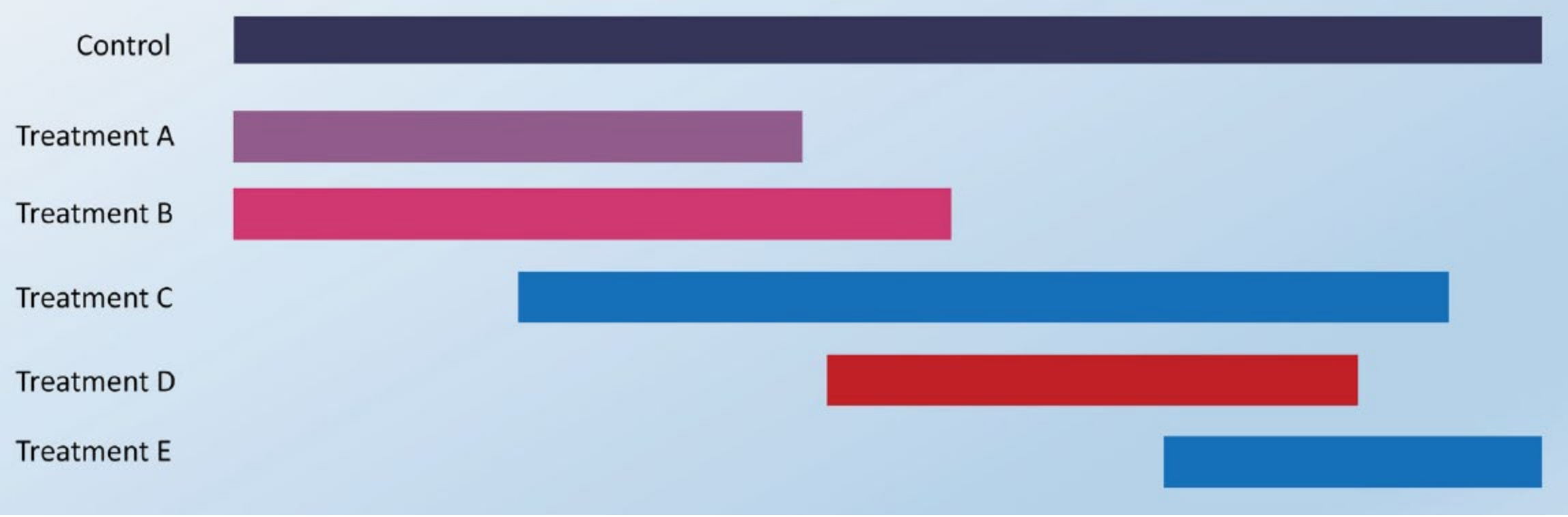
- Control treatment may change in the second or third RCTs.
- Simple and easy to interpret.

New arm introduction is not considered in general.

- Groups sequential monitoring may allow interim treatment selection.
- If new arm introduction is invoked, the trial design may become complex.

Open platform trials

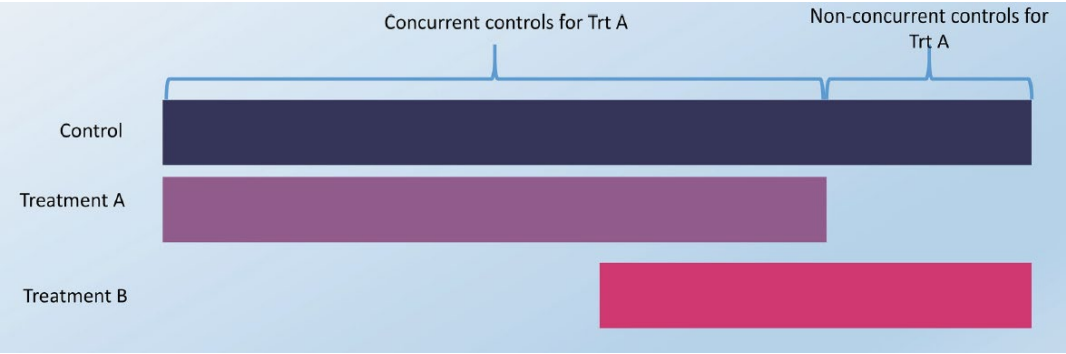
New arm(s) introduction (arms C-E) is allowed.



Different analytic strategies to use control data

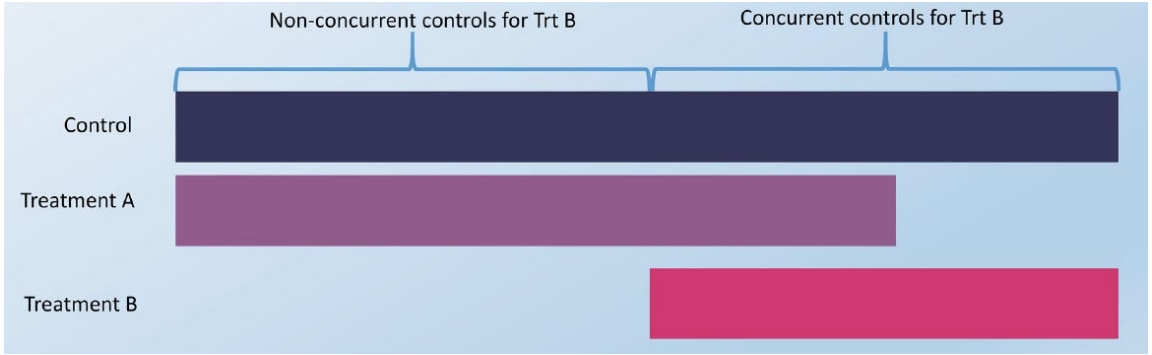
Concurrent control

- Some control pts are discarded from control-trt A comparison.
- Valid inferences due to randomization.



Non-concurrent control

- Efficient use of existing data.
- Invalid inference due to non-randomized controlled pts.



Other modifications of platform trials

More complex and adaptive!!

- A Bayesian modeling approach which enables the followings.
  - Response adaptive randomization;
  - Borrowing strengths from internal or external data;
  - Hierarchical modeling between multiple disease subtypes or biomarker-defined subsets;
  - Modeling surrogate and true endpoints for imputing missing data.
- Time machine for comparing non-concurrent control and test arm
  - A modeling technique used to estimate how a control arm has evolved over time.
  - Incorporation of time trends in non-concurrent control

Embedding

- Collecting data in a more routine clinical practice (e.g., electrical health records)

How to assess statistical complexities?

Statistical OCs of clinical trials

- Type-I error rate, power, bias and variance of estimated treatment effects
- Average sample size if interim analyses are planned.

For simple closed platform trials, evaluation of OCs can be easy.

For complex open platform trials, evaluation may be difficult.

- Extensive simulation is needed.
- Simulation reports should be assessed by regulatory bodies, if needed.
- Education of statistically complex issues for non-statistical experts is also important.

Fig: Lavange L, et al. Annals Intern Med 2021.

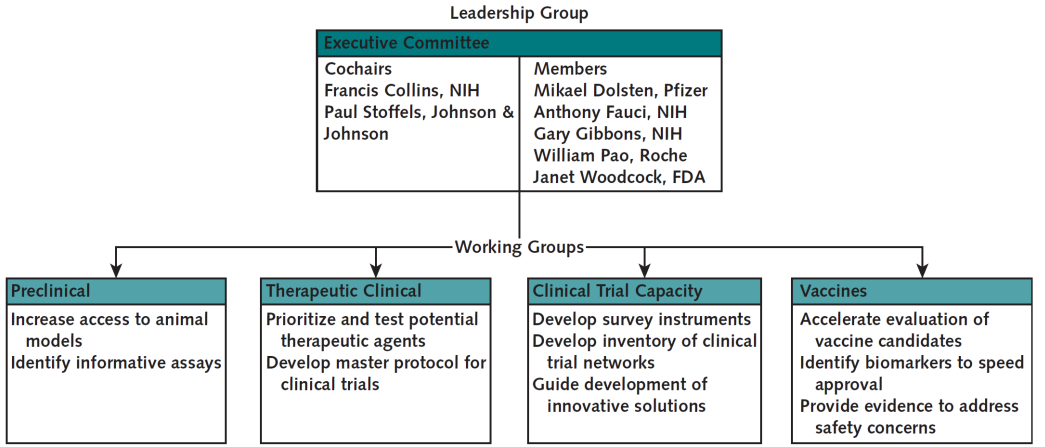
Logistical issues

The use of common organizations and procedures in one master protocol can be a less redundant approach.

- Teams for protocol development and selection of therapeutic candidates;
- DMCs and other related organizations.

Who holds leadership positions of many collaborators?

- Multiple pharma, CROs, research organizations, committees for clinical trials, funders
- A case example of ACTIV trial
  - NIH & CDC sponsored
  - ACTIV partnership
    - U.S. government (incl. FDA)
    - academia
    - 18 pharma, and so on



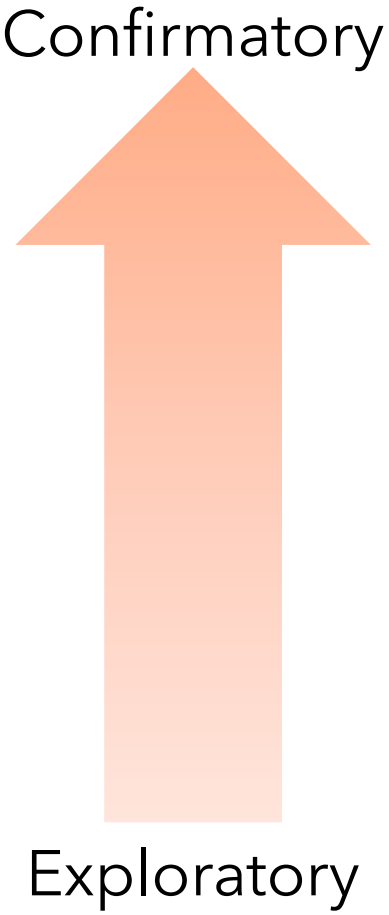
Level of confirmatory nature

Closed platform with conventional analysis methods / open platform using concurrent control only

- Suitable for the primary analysis in the pivotal trials
- Highly likely to gain a regulatory approval

Open platform using several complex ideas

- Not suitable due to the exploratory nature
- Less likely to gain a regulatory approval



Complex innovative trial design (CID) @FDA

CIDs: no fixed definitions

- CIDs referred to as *complex adaptive, Bayesian, and other novel clinical trial designs* in PDUFA VI commitment letter.
- Designs that have rarely or never been used.

Recently, there are great expectations for CIDs, but …

- Limited use;
- Lack of clarity regarding regulatory acceptance and guidance;
- Lack of experience and understanding;
- No chance to publicly discuss CID proposals.

CID paired meeting program

Prescription drug user fee act VI (PDUFA VI; 2018-2022)

- CID pilot meeting program (5 yrs)
- FDA selected 2 submissions from sponsors per quarter.
  - Sponsors had the opportunity to discuss with regulatory team.

Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

Guidance for Industry

PDUFDA VII (2023-2027)

- Continuation of CID paired meeting program
  - FDA will select up to 8 proposals per year.
- For promotion purposes, CIDs through the program may be presented by FDA (e.g., in a guidance or public workshop).

https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

Price D and Scott J. Clin Trials 2021.

Case studies of CIDs

#1: Duchenne muscular dystrophy デュシーヌ型筋ジストロフィー症

- Placebo versus low/high doses RCT
- Bayesian MMRM, sample size re-estimation, treatment selection, response adaptive randomization, hybrid control approach

#2: Pediatric multiple sclerosis 小児多発性硬化症

- 2-armed RCT (non-inferiority)
- Bayesian negative-binomial model, meta-analytic predictive prior from adult data

#3: Multiple interventions across multiple pain conditions　慢性疼痛

https://www.fda.gov/media/155403/download

- Multiple placebo-controlled RCTs（sub-study）
- Bayesian hierarchical model to leverage placebo and treatment effect information.

https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

Case studies of CIDs

#4: Systemic lupus erythematosus　全身性エリテマトーデス

https://www.fda.gov/media/155404/download

- Placebo versus 3-doses RCT
- Response adaptive randomization, futility monitoring and dose selection

#5: Population: Diffuse large B cell lymphoma　びまん性大細胞リンパ腫

https://www.fda.gov/media/155405/download

- Hybrid control approach (2-armed RCT, 2:1 ratio)
- Assess secondary endpoint of OS by using propensity score matching and Bayesian survival analysis methods.

https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

High hurdle for Japanese platform trials

Limited governmental leadership and funding

Limited experiences for CIDs

- Statisticians and clinical teams in academia and pharma
- Regulatory may have few experiences

Several difficulties for global expansions

These do hinder ambitious and challenging Japanese platform trials.

Please enjoy our symposium!!

Dr. Lori will come back to Japan on March 2023.

@ 日本臨床腫瘍学会 https://site2.convention.co.jp/jsmo2023/

Date and time: March 18th, 10:10–11:40 (total, 90min)
Language: English
Chairperson: Dr. Yasuhiro Fujiwara (Chief executive of PMDA)
Dr. Shogo Nomura (The University of Tokyo)

Keynote lectures (30min including 5min Q&A, each)

(1) Future perspectives on platform trials
by Dr. Lori E Dodd (National Institute of Allergy and Infectious Diseases)

(2) The use of external control arm for premarket programs
by Dr. Elizabeth Lamont (Medidata Solutions)