The Utility of Adaptive Design Clinical Trials for Vaccines

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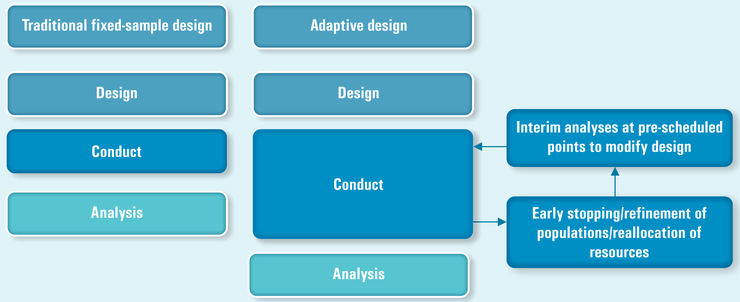
Background

- Randomized controlled trials (RCTs) are the gold standard for reducing bias and confirming causality.[1]
- Their inflexible, fixed designs limit adaptability, delay timelines, and reduce efficiency.[1]
- Adaptive design clinical trials (ADCTs) enable pre-specified changes based on interim data, improving trial flexibility while maintaining scientific validity.[2]
- ADCTs are particularly helpful during vaccine development, facilitating real-time adjustments to optimize candidates, doses, and populations, such as during public health crises, like COVID-19.[2]
- ADCTs enable rapid decision-making and resource reallocation, expediting access to safe and effective vaccines.[2]

History and evolution of ADCTs

- Adaptive designs originated in the 1970s, progressing through adaptive randomization, group sequential designs, and sample size re-estimation.[2]
- The 1990 introduction of the continuous re-assessment method (CRM) offered better toxicity control and dose optimization in early-phase trials.[2]
- Adaptive designs have since expanded to address various trial needs, including changes in allocation, sample size, study termination, hypotheses, and combined approaches.[2]
- They are classified based on the trial elements being modified, enabling a tailored and receptive approach to different research goals.[2]

Differences between traditional RCT design and an adaptive design[2,3]



Compared to traditional RCTs, ADCTs reduce patient exposure to ineffective or harmful treatments and can complete trials faster with fewer participants.

Adaptive Trial Design[3]	Concept/ Idea[3]	Examples of Studies (and also Vaccine trials) where the design was used
Adaptive Randomization	Patient allocation based on interim data to favour more effective treatments.	• BATTLE Trial (2011), a lung cancer study • COVID-19 Vaccine Trials-Moderna's Phase III trial (2021)
Group Sequential Designs	Interim analyses enable early termination of the trial due to concerns regarding efficacy, futility, or safety.	• ISIS-2 Trial (1998), a study monitoring the effect of aspirin and streptokinase on mortality after myocardial infarction • H1N1 Influenza Vaccine Trials (2009)
Seamless Phase II/III Designs	Combines phases II and III into a single continuous trial, reducing development time.	• I-SPY 2 Trial (2019), a breast cancer trial • Ebola Vaccine Trials-The "Ebola ça suffit!" trial (2015)
Sample Size Re-estimation Designs	Sample size adjustments during the trial based on interim analysis to maintain statistical strength.	• MUSEC Trial (2012), a multiple sclerosis study • Malaria Vaccine Trials (2008)
Adaptive Dose-Finding Designs	Dose level adjustments based on interim safety and efficacy data to confirm the optimal dose.	• CRM (Continual Reassessment Method)-Various oncology studies (2020) • COVID-19 Vaccine Trials-Pfizer-BioNTech's BNT162b2 early-phase trial (2020)
Bayesian Adaptive Designs	Applies Bayesian statistics to revise the probability of treatment success with the accumulating data.	• SMART Trial (2024)-Evaluating different measures for managing chronic care • TB Vaccine Trials (2017) • PREVAIL II Trial (2016) - for Ebola treatment
Response-Adaptive Designs	Treatment allocation is modified to maximize patient benefit as per the responses observed during the trial.	• EPIC Trial (2018), a study among HIV patients
Platform Trials	Evaluates multiple treatments simultaneously within a single trial to refine population based on interim results.	• RECOVERY Trial (2020-21) - COVID-19 treatment trial
Biomarker-Adaptive Designs	Biomarker information is used to customize treatment to subgroups of patients.	• TAILORx Trial (2018), a breast cancer trial • HPV Vaccine Trials (2015)

Current challenges in vaccine development and approaches to overcome them[2–4]

Challenges in Vaccine Development	How ADCTs Help Overcome These Challenges
Long development timelines (10-15 years)	Adaptive designs allow early stopping or rapid progression, saving time and resources.
Unpredictable outbreaks	Flexibility to quickly adapt to emerging needs or pathogen variants without major protocol modifications.
Difficulty identifying at-risk populations	Response-adaptive and biomarker-adaptive designs dynamically refine population selection.
Complex dosing and safety protocols	Dose-finding and Bayesian designs optimize dosage using real-time data, which is particularly important in evaluating immune responses
Variable vaccine efficacy across groups	Seamless Phase II/III and platform trials allow stratified assessments efficiently.
Rare adverse events impacting confidence	Group-sequential and adaptive monitoring enable early safety signals and adjustments.
Rapid viral mutations (e.g., SARS-CoV-2)	Platform and Bayesian designs can test multiple formulations and adapt in real time.

Regulatory concerns about ADCTs and approaches to overcome them[2–4]

Regulatory Challenges	Methods to overcome challenges
Concerns about trial validity, reliability, and acceptable adaptation levels	Transparent documentation and pre-defined adaptation plans support scientific integrity.
Uneven global guidance; only USFDA and EMA offer detailed frameworks	Promoting global uniformity and training using existing FDA/EMA frameworks.
Risks of operating bias, deferred planning, and complex consent	Using educational programs to improve clarity for investigators, ethics committees, and patients.
Inconsistent understanding among stakeholders	Providing-simple, multimedia-based learning resources-tailored for diverse stakeholders.
Concerns about unblinding, sample size shifts, and cost	Pre-planned simulations and robust data handling to ensure trial credibility and cost-efficiency.
Lack of awareness of ADCT benefits	Regulatory-sponsor partnerships for awareness-building and contextualized guidelines.
Misconceptions leading to biased rejection	Sharing successful ADCT case studies (e.g., PREVAIL II, COVID-19 trials) to increase adaptability.

Perspectives of Regulatory Agencies on ADCTs[5–7]

- Both USFDA and EMA emphasize transparency and justifications for adaptations.
- Both regulatory bodies have strongly supported ADCTs, particularly in case of validated designs that can adequately address queries regarding type 1 error rate control and bias.

USFDA underscores early engagement with sponsors, especially during drug development

EMA advises vigilant use of ADCTs, especially in late-stage trials

An overview of global regulatory frameworks for adaptive trial designs in research[5–7]

Region/ Organization	Regulatory bodies and their key Guidelines (Name)	Focus Areas: Adaptive elements	Statistical methods & accuracy	Trial integrity	Adaptive designs in Confirmatory trials	Protocol changes	Interim analysis	Patient safety	Regulatory oversight & flexibility	Trial design efficacy	Data monitoring	Study design flexibility	Ethical considerations	Harmonized guidelines across regions	Design analysis & planning	Global health impact
	USFDA-Adaptive Designs for Clinical Trials of Drugs and Biologics (2019)	✓	✓	✓	–	–	–	–	–	–	–	–	–	–	–	-
	EMA-Reflection Paper on Methodological Issues in Confirmatory Clinical Trials with Adaptive Designs (2007)	–	✓	–	✓	✓	–	–	–	–	–	–	–	–	–	-
	MHRA-Guidance on the Use of Adaptive Designs in Clinical Trials (2012)	–	–	–	–	–	✓	✓	✓	–	–	–	–	–	–	-
	NMPA - Technical Guidelines for Adaptive Design in Clinical Trials (2019)	–	–	–	–	–	–	–	✓	✓	✓	–	–	–	–	-
	TGA - Guidance on Clinical Trials: Adaptive Designs (2019)	–	✓	–	–	–	–	–	–	–	–	✓	✓	–	–	-
	ICH E20: Adaptive Clinical Trials (2019)	–	–	–	–	–	–	–	–	–	–	–	✓	✓	✓	-
	WHO - Ethical Considerations for the Use of Adaptive Clinical Trial Designs (2023)	–	–	–	–	–	–	–	–	–	–	✓	✓	–	–	✓

Successful implementation of adaptive designs for vaccine approvals

HPV Vaccine Trial (2015)
Seamless phase 2b/3 ADCT enabled dose selection after interim analysis, fast-tracking HPV vaccine development with regulatory coordination.


Design
CLINICAL TRIALS
A seamless Phase IIB/III adaptive outcome trial: Design rationale and implementation challenges
Y H Joshua Chen[1], Richard Gesser[1,2] and Alain Luxembourg[1]
Clinical Trials 2015; Vol. 12(1) 84–90
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DOI: 10.1177/1740774514552110
ctj.sagepub.com
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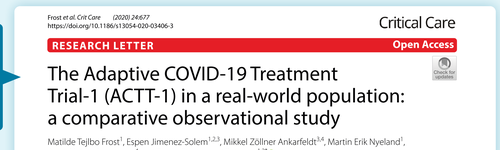
RECOVERY-RS Trial (2022)
Multi-arm ADCT rapidly assessed three non-invasive ventilation methods for COVID-19, optimizing recruitment and data collection across centers.


JAMA | Original Investigation
Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19
The RECOVERY-RS Randomized Clinical Trial
Gavin D. Perkins, MD; Chen Ji, PhD; Bronwen A. Connolly, PhD; Keith Couper, PhD; Ranjit Lall, PhD; J. Kenneth Baillie, PhD; Judy M. Bradley, PhD; Paul Dark, PhD; Chirag Dave, MD; Anthony De Soyza, PhD; Anna V. Dennis, MBBS; Anne Devrell, BPhil; Sara Fairbairn, MB, BCh; Hakim Ghani, MSc; Ellen A. Gorman, MB, BCh; Christopher A. Green, DPhil; Nicholas Hart, PhD; Siew Wan Hee, PhD; Zoe Kimbley, MB, ChB; Shyam Madathil, MD; Nicola McGowan, MRes; Benjamin Messer, MA; Jay Naisbitt, MB, ChB; Chloe Norman, PGCE; Dhruv Parekh, PhD; Emma M. Parkin, MSc; Jaimin Patel, PhD; Scott E. Regan, BA; Clare Ross, MBBS; Anthony J. Rostron, PhD; Mohammad Saim, MBBS; Anita K. Simonds, MD; Emma Skilton, BSc; Nigel Stallard, PhD; Michael Steiner, MD; Rama Vancheeswaran, PhD; Joyce Yeung, PhD; Daniel F. McAuley, MD; for the RECOVERY-RS Collaborators

ACTT-1 Real-World Comparison (2020)
ACTT-1 findings were translated to real-world settings using digital RWD, bridging trial results with clinical practice during the pandemic.


Frost et al. Crit Care (2020) 24:677
https://doi.org/10.1186/s13054-020-03406-3
Critical Care
RESEARCH LETTER Open Access
The Adaptive COVID-19 Treatment Trial-1 (ACTT-1) in a real-world population: a comparative observational study
Matilde Tejlbo Frost[1], Espen Jimenez-Solem[1,2,3], Mikkel Zöllner Ankarfeldt[3,4], Martin Erik Nyeland[1], Anne Helms Andreasen[4] and Tonny Studsgaard Petersen[1,2*]

REMAP-CAP + LOVIT-COVID Harmonization (2020)
Two trials were adaptively merged to assess Vitamin C in COVID-19, enabling unified analysis and evidence generation across platforms


Research
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Intravenous Vitamin C for Patients Hospitalized With COVID-19
Two Harmonized Randomized Clinical Trials
The LOVIT-COVID Investigators, on behalf of the Canadian Critical Care Trials Group, and the REMAP-CAP Investigators

Future directions[2–4]

- ADCTs are a promising, robust alternative to traditional RCTs, especially in vaccine research.
- They facilitate protocol amendments based on interim data, providing flexibility in unpredictable circumstances, like pandemics.
- ADCTs can simplify regulatory approvals by allowing real-time assessment of safety and efficacy, and assessment of multiple therapies.
- Regulatory agencies like the USFDA and EMA support ADCTs with detailed supplementary guidance documents.

Conclusion

- Regulatory approval of ADCTs depends on sponsors' ability to validate adaptations that are ethically sound and scientifically accurate.
- Successful implementation necessitates stakeholder education and awareness, realistic guidelines, and collaboration among sponsors, researchers, and regulators.
- Compared to traditional RCTs, ADCTs can accelerate vaccine development to facilitate quicker access to safe and effective vaccines.

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