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GATES foundation

DESIGN,
ANALYZE,
COMMUNICATE



DAC Assessment Tool Modified for COVID-19 Studies

*Principles and approaches for research methods to
Design, Analyze, Communicate (DAC) clinical studies*

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Purpose of document

The purpose of this document is to enable a rigorous and standardized review and subsequent discussion of a clinical trial to enhance the probability of having an informative and efficient study. While always true, this is especially critical during a pandemic. Study teams should use this reference to clarify thinking around design, analysis and communication aspects and if appropriate share this information with potential funders and/or collaborators. Addressing these questions upfront will facilitate a more efficient review by necessary parties.

Introduction

Clinical studies represent very significant investments of time and money and in a pandemic setting both are in short supply increasing the urgency to think along the lines of the questions included in this tool. They are a major source of information regarding go/no-go decisions, regulatory approval, health economics and outcomes research (HEOR), policy determinations and ultimately patient access and public health benefits. Unfortunately, it is well documented that not all clinical studies provide robust answers to the questions being addressed. Inadequate design and analysis (for which there are a number of different causes¹) can lead to erroneous or meaningless results – deemed “uninformative” by some. Currently, there are numerous COVID-19 clinical studies ongoing or having been reported that fall into this “uninformative” category. This leads to rejecting medicines or strategies that could have impact, as well as wasting scarce resources. Furthermore, these uninformative or even inefficient studies can erode trust between investigators and patients.²

Creating efficient and informative clinical studies requires a team of qualified specialists. Frequently this includes but is not limited to principal investigators, experts in the given disease, pharmacologists, pharmacometricians (where the intervention is a drug or requires a dose and regimen selection), statisticians and operational experts.

This document is a list of important elements to be considered in **the design, analysis and communication (DAC)** of clinical studies (regardless of stage of development of the medicine or intervention). It is intended to serve as a tool to structure critical discussions prior to committing substantial human and financial resources and enrolling human subjects. While not all points are relevant to all studies, in general they are intended to promote sound and proven scientific methodology combined with the use of more recent innovations in trial design.

¹ <https://bmcmredsmethodol.biomedcentral.com/track/pdf/10.1186/1471-2288-12-60>

² JAMA. 2019;322(9):813-814. doi:10.1001/jama.2019.9892

Our intention is to promote a set of “best practices” to assist the entire COVID19 clinical trial ecosystem towards a rapid and informed decision-making endeavor that will save lives during this critical period.

Instructions for completing this document

Please provide comprehensive responses to the questions in this document. It is not intended that answers replicate existing study documents where the questions are clearly answered in the protocol (or other relevant documents, e.g. investigator brochure). Where this is the case, a brief orientating response plus cross reference to the relevant section in the pre-existing document is acceptable. Similarly, where appropriate, cross refer between answers in this document, to aid response and avoid duplication. Please also explain acronyms.

GENERAL ASPECTS

1. What is the **purpose** of the study (e.g. exploratory, regulatory pathway/approval, non-regulatory product intervention, health technology assessment (HTA), policy change, health system strengthening)?

What is the proposed **scientific question** to be addressed by the study? Explain how the study will clearly answer or better inform the scientific question.

2. Outline how the proposed study fits into the overall **development or life cycle strategy** for the product or intervention. How will this build on the **existing knowledge** base with this use and what new information will this provide?
3. If the study is successful, what would the next steps be? Specifically, what decision will be made based on the results of this study. Describe the plans for dissemination of researching findings
4. Please detail the **external** (to your organization) advice you have received or plan to seek in the design of this study, including regulatory/scientific, policy, ethical, and implementation aspects. Summarize if you have solicited or received advice from local experts on insights in areas of epidemiology – especially relevant to COVID19, existing interventions, standards of care relevant to the health system or population of interest and conduct of studies in the setting you propose.
5. What, if any, disease-specific or clinical study guidelines are you consulting and proposing to follow (e.g. FDA/EMA/WHO including the various R&D blueprint documents/ICH/ in the design of this trial? NOTE, many regulatory agencies have created expedited means to obtain feedback on COVID19 specific

protocols. Please describe and discuss the regulatory pathway you are proposing to use for approval of this study.

6. Is there appropriate **governance** in place (e.g. appropriately constituted study steering group, Data Safety and Monitoring Board (DSMB) and associated Charter? What is the focus of each group and what decisions will each be responsible for making? Is there sufficient experience on the various governance board for this specific study?
7. Describe what you see as the limitations / challenges of this proposed study and potential mitigation.
8. Discuss your choice of site selections (number of sites, number of countries). Will the results be generalizable to multiple countries or regions?

DESIGN ASPECTS

9. Summarize your study design inclusive of objectives, assessments and endpoints.
10. Describe how the proposed **eligibility criteria** relate to the population suffering from/at risk of the disease/condition. Will any restrictions in eligibility affect generalizability?
11. How do the primary and secondary **endpoints** address the scientific questions and purpose(s) of the trial? Are the endpoints appropriately validated and accepted. Are these the same endpoints as being used in other studies, e.g. WHO master protocol? If not, please explain why not.
12. Is the **duration** of the study adequate to answer the scientific question, considering the anticipated clinical efficacy effect, as well as expected duration of effect and risk of treatment failure/relapse? Please include consideration of any unique characteristics that your target population or investigational agent may have.
13. What is the **basis for the effect size** estimate?? Is the proposed effect size clinically relevant? Have assumptions on effect size been considered, including likely severity of disease to be enrolled into the study, based on inclusion/exclusion criteria?
14. If the study will test a drug, vaccine, or therapeutic intervention (including trials of disease prevention), describe and justify the **dose selection criteria and dosing regimen**. Please provide background documentation into the pharmacokinetic/pharmacodynamic (PK/PD) assessments or other

- dose/regimen ranging that support the dose and regimen selection or other references supporting the proposed dose(s).
15. Provide a detailed description of the **simulations** that were conducted as a part of developing your proposed study design and include the associated code if applicable. Explain how the simulations support your design as the best one to implement (e.g., adaptive and/or factorial allows testing of multiple doses/interventions). Have simulations been run on the likely response rates/disease prevalence/incidence/likely variability of the data/ability to follow up patients etc? If so, please describe. If simulations were not conducted, please explain the decision not to do so.
 16. What is the basis for the **sample size** calculation?
 17. Describe the **mechanism of action** of the investigational agent or intervention and describe whether it is sufficiently clearly understood to justify the proposed study design.
 18. Provide detail about the proposed study location(s) and describe how the **disease burden and epidemiology at the proposed study location(s)** is appropriate to enable the trial to address the study question and is consistent with the operational timelines.
 19. Describe your plans for **PK sampling** during this study relating results to what is already known about the PK of the test medicinal product. How will this be linked with PD effect/efficacy measures/adverse reactions?
 20. Describe your plans (inclusive of participant consent) for any **biological sampling, analysis and storage**.
 21. If using a product as the **comparator**, is it being used consistent with its approved indication from a stringent regulatory agency and/or WHO prequalification?
 22. Explain how the potential for interactions (e.g. drug-drug or between agents in the study/or food effects or other substances recipients may receive) has been considered and addressed in your design.
 23. Describe the **randomization method**, including type of randomization and any restrictions and methods used to implement. If not randomized, please explain how you will put the results into context/interpret whether they are meaningful or not.

24. Will this study enroll **special populations** including elderly/ /pregnant women/nursing mothers? If so, have appropriate safety considerations been given to these populations? .
25. Detail the main sources and types of **bias** during the study and how these will be minimized.
26. Describe your **safety monitoring** plan inclusive of any safety aspects that require specific monitoring.

ANALYZE ASPECTS

27. Provide your **statistical analysis plan** for the study including the method for subject allocation, measurement methods of response variables, hypothesis to be tested, analytical approach to common problems including early study withdrawal and protocol violations.³
28. Describe your **interim analysis plans** inclusive of decision rules/stopping rules, possible outcomes and statistical adjustment considerations. Please describe any pre-planned adjustments to the study design (e.g. adaptive designs) and operating characteristics of the decision rules related to the adaptive elements of the design.
29. Describe how **compliance** with treatment is being measured and analyzed. What do we know about compliance with the intervention in this patient population? How will measures of compliance be assessed in the analysis?

COMMUNICATE ASPECTS

30. Describe your community **engagement strategy and communication plans**. How will you include **local community** members in your study team (i.e., to ensure robust understanding of local culture and considerations, and improve communication)? Describe the ways that you will prioritize information sharing and engagement before, during and after the study with the following groups: study participants, their families, community leaders, communities, local health systems, policy, regulatory and Ethics committees, Institutional Review Boards, Data Safety & Monitoring Boards, and Patient Advocacy Boards. Please also define the start and end date, and sub-phases for each of the communication phases in this study.
31. Describe your plans for **study consent (or alternatively community assent)**, inclusive of data reuse, biological sampling and analysis and communication, to make study participants aware of how study decision rules could impact them. Will you ensure the informed consent form will be in local languages and dialects? How will you handle consent for illiterate participants?

³ ICH E8 NOTE FOR GUIDANCE ON GENERAL CONSIDERATIONS FOR CLINICAL TRIALS

32. If a multi-site study, please describe your **cross-site communication** and collaboration plan that ensures alignment of study site protocols, clinical operations training, data collection, data standardization, and data sharing.
33. What is your plan for **communication with local study workers** before, during and after the study?
34. On which publicly accessible database will your **study be registered**?
Note: Examples of globally recognized existing standard registries include ISRCTN, clinicaltrials.gov, or the Pan-African Clinical Trials Registry. It would be expected that registration would be on one of the WHO compliant registries.
35. Describe your commitment and plans to **publish** study results as soon as is practical, regardless of outcome, as well as your forecast of when the publication will be submitted following database lock. Describe your plan to publish your raw, most granular study data and associated code, such that, when the code is run by a third party on the data package provided, the third party will be able to reproduce your test statistic values. Describe your policy for reuse of your data for secondary analysis by the public, including how you will facilitate reproducible **data-sharing**.

OTHER REFERENCES:

See also

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8-general-considerations-clinical-trials>

HELP:

As this tool is meant to foster a dialog between various stakeholders, please feel free to reach out with questions regarding the use of this tool by using the following email address: DACtrials@gatesfoundation.org.

APPENDIX 1

2020 DAC PILLARS LIST

What are DAC Pillars? DAC Pillars are clinical study best practices that can make BMGF investments more informative.

#	Type	Sub-Type	DAC Pillar
1	Design	Epidemiology	Prioritize disease burden/target epidemiology as criteria for trial site selection
2	Design	Epidemiology	Analyze real world evidence to optimize study investments, objectives, and feasibility
3	Design	Epidemiology	Use common endpoints for target pathology
4	Design	Epidemiology	When appropriate, proactively map study outcome to policy impact
5	Design	Statistics	When feasible, apply adaptive, pragmatic, and factorial clinical trial designs
6	Design	Statistics	Simulate trial to ensure right sample size and optimal design
7	Design	Statistics	Publish study protocol and analysis plan in open-access resource
8	Analyze	On Inception	Develop and apply a prospective, fixed statistical analysis plan
9	Analyze	Ongoing	Use interim analyses with stopping for success or futility
10	Analyze	Ongoing	When appropriate, use model-informed drug development, such as PK/PD modeling
11	Analyze	Ongoing	When appropriate, implement real-time data analysis capability
12	Communicate	Locally	Develop study consent language that respects individuals, advances research, promotes health and fosters trust
13	Communicate	Locally	Include local community members in the study team to understand local culture and considerations
14	Communicate	Locally	Engage local regulators/ethicists, insuring they have content to review and monitor the study details
15	Communicate	Locally	Implement a communication plan that speaks to participants, families, communities, and health systems before, during, and after the study
16	Communicate	Globally	Publish study results in open access resource, regardless of outcome, with raw study data and code to enable reproducibility and reuse