DESIGN,
ANALYZE,
COMMUNICATE DAC

DAC Assessment Tool

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

Ian Hudson, Thea Norman, Shawn Dolley and Dan Hartman
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Purpose of document

This Design, Analyze, Communicate (DAC) Assessment Tool (DAT) questionnaire is intended to be filled out by Principal Investigators (PI) during study planning: the answers to the questions can be used to structure critical discussions with various study stakeholders.

Introduction

Clinical studies represent very significant investments. 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 causes[1]) can lead to erroneous or meaningless results – deemed "uninformative" by some. This leads to rejecting medicines or strategies that could have impact, as well as wasting scarce resources. Furthermore, these uninformative studies can erode trust between investigators and patients.[2]

Creating 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. Many global health studies supporting advances in healthcare in LMIC countries also require local input.

The DAT questionnaire is a list of important elements to be considered in **the design, analysis and communication** of clinical studies (regardless of stage of development of the medicine or intervention). It is also 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.

It is recognized that there are several aspects of high relevance to ensure rigorous clinical study design, analysis and communication (please see Appendix 1, DAC best practices for informativeness). Consider the DAC Best Practices when discussing your answers.

[1] https://bmcmedresmethodol.biomedcentral.com/track/pdf/10.1186/1471-2288-12-60
[2] JAMA. 2019;322(9):813-814. doi:10.1001/jama.2019.9892

GENERAL ASPECTS

1. What is/are the **scientific question(s)** to be answered by the study? Explain how the study will clearly answer or better inform the scientific question(s).

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 and what new information will this provide?

3. What is the **purpose** of the study (e.g., regulatory pathway/approval, new application or extension of existing license, non-regulatory product intervention, health technology assessment (HTA), policy change, health system strengthening)? What decision, clinical program advancement, policy or policy change, would a positive outcome in your study help to support?

4. Please detail the **external (to your organization) advice** you have received or plan to seek in the design of this study, including regulatory authority/scientific, ethical, and implementation aspects. If the study is aimed towards a change in health policy, have you engaged with policy makers to understand their requirements, concerns around implementation, costs, politics and acceptability early enough to have those questions factored into or answered in the study? Have you solicited or received advice from local experts regarding epidemiology, existing interventions, standards of care relevant to the health system or population of interest and conduct of studies in the setting you propose? If so, please describe the findings.

5. What, if any, disease-specific or clinical study **guidelines** are you consulting and proposing to follow (e.g., FDA/EMA/WHO/ICH/HTA) in the design of this trial?

6. Please describe the **study governance** that is proposed for this study (e.g., appropriately constituted Study Steering Group, Scientific Review Committee, Data Monitoring Committee and associated Charters). What is the focus of each group and what decisions will each be responsible for making?

7. Describe what you or others see as the **limitations, challenges, and risks** of this proposed study. Please summarize your mitigation plans for each.

8. Describe your **rationale and site selections** (number of sites, number of countries, and country names). How will the results be generalizable to multiple countries or regions?

9. Describe your plans for **study monitoring**, ensuring data integrity and quality management. Please also describe your **data collection and management plans**. Are you planning to use digital data collection tools? If so, have they been appropriately validated and certified?

DESIGN ASPECTS

10. Summarize your **study design** inclusive of objectives, assessments and endpoints.

11. Describe how the proposed **eligibility criteria** relate to the population suffering from/at risk of the disease/condition. What steps will you take to ensure as diverse and representative a population as possible and appropriate will be included in this study? Will any restrictions in eligibility affect generalizability? Conversely, are you planning on restricting eligibility and enriching the population to maximize the chance of demonstrating efficacy? If so, please expand on the reasons. Are the chosen geographies able to identify sufficient patients meeting the eligibility criteria? If this is a cluster randomized trial, what eligibility criteria will apply to clusters?

12. Will this study enroll **special populations** including elderly/children/pregnant women/nursing mothers? If so, have appropriate safety considerations been given to these populations? Is the target population for clinical use likely to include these groups?[3,4] If these special populations are excluded from the study, yet experience the disease, discuss how this gap will be addressed, and how this will affect the product label or policy considerations on the use of the intervention in this population.

13. How do the primary and secondary **endpoints** address the scientific questions and purpose(s) of the trial? Are the endpoints appropriately validated and accepted? If so, how (e.g., reference regulatory guidelines that specify the proposed endpoints or provide peer-reviewed publications of similar or precedent studies that use the same endpoints)? Please also describe the rationale for the selection of the **time period** for measuring the endpoints. If no validated/accepted endpoints exist, please detail the input and alignment on your endpoints that you have received from key disease area stakeholders (e.g., disease area researchers, policy makers) and any limitations this poses to the potential subsequent value of this study.

14. **Endpoint** methodology, variability and timing: Describe the **methodology** for assessing the primary and key secondary endpoints. Is this methodology generally accepted? Describe what is known about **variability** of the primary and secondary endpoints (where appropriate). Consider diurnal variability, seasonal and geographic variability, measurement variability, spatial variability (if cluster randomized) and intra-person variability over time. What are strengths and limitations of these endpoints regarding the consistency with which they may be ascertained in study subjects? For endpoints that are

[3] https://database.ich.org/sites/default/files/E7_Guideline.pdf
[4] https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf

based on lab data that are non-routine (e.g., antibody titers and other biologic assays) and if the sample analysis is not done in a single central lab, are the methods validated across the labs?

15. Is a **run-in time period** required, and if so for how long and why? Will you use it to correct for/ improve inputs on actual site-specific burden of disease, recruitment rates, and other potential inputs?

16. Describe how the **duration** of the study is 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. [For Vector Control interventions, are there plans to monitor durability and efficacy over the life of the product?]

17. What is the **basis for the effect size** estimate used to power your study? Describe the current data (noting when generated) in a relevant setting that justifies the response rates and explain if/how it varies depending on the severity of the disease. What efforts have been made to ensure the estimate is not inflated? Have assumptions on effect size been considered, including likely severity of disease to be enrolled into the study, based on inclusion/exclusion criteria? What is the minimally clinically relevant effect size and is the study powered to detect it?

18. What is the basis for the **sample size** calculation? Does the protocol allow for adjustment of sample size based on review of event rates at baseline, during a run-in period, or during the study?

19. Describe the **randomization method**, including type of randomization, stratification factors and other features of the randomization scheme and any restrictions and methods used to implement.

20. 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.

21. Describe how you have considered the design and outcomes of **previous studies** and/or **real-world evidence** in the design of this study (please include references to those studies and/or the sources of real-world evidence data that was used). If any of these studies were of poor design or had other weaknesses, explain how you plan to address these aspects in your design.

22. If the study will test a drug, vaccine, or therapeutic intervention (including trials of disease prevention), describe the **dose selection criteria**. 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). Is it currently licensed and being used in accordance with the license/standard of care? If not, do you envisage any changes before further studies?

23. Describe the **mechanism of action** of the investigational agent or intervention and how that is relevant for the proposed use.

24. Describe how the study plan **accounts for gender** in determining target population, eligibility criteria, effect size estimate and dosage/dosing regimen. If you are not considering gender as a variable, please explain why. Is this study testing for **gender differentiation or covariate gender effects**? If yes, please explain your plans for sample size and randomization techniques. If no, please provide a rationale.

25. 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.

26. 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?

27. If using an **active comparator** as control, is it being used consistent with its approved authorization from a stringent regulatory agency and/or WHO prequalification?

28. 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) have been considered and addressed in your design.

29. Detail the main potential sources of **bias** during the study and how these will be minimized.

30. What **provisions** have been made for patients failing treatment and any who may require long term treatment?

31. Please describe your plans for **blinding** the study. Please describe who will and will not be blinded to study treatment

32. Describe your **safety monitoring** plan including any safety aspects that require specific monitoring and/or mitigation action and/or selection of sites with appropriate facilities. How will safety alerts be handled? [For Vector Control interventions or genetically modified organisms, are there plans to monitor ecological/environmental impact and minimize any impact? How will interventions be disposed of at the end of the study?]

ANALYZE ASPECTS

33. Provide your **statistical analysis plan** (draft, if not finalized) 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.[5] Please describe your plans to analyze and report disaggregated data by gender, including data for withdrawals or dropouts.

34. Describe your **interim analysis plans** including decision rules/stopping rules, possible outcomes, and statistical adjustment considerations. Will there be criteria to stop for futility or efficacy? If not, please explain the rationale. 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.

COMMUNICATE ASPECTS

35. Describe your **Community Engagement Strategy and Communication Plan,** including timings. 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)? What forms of communication (e.g., social media, print, webinars) are best suited to the study communities?

36. Describe your plans for **study consent (or alternatively community assent)**, including allowing data reuse and biological sampling.

37. 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 cross-site data sharing.

38. On which publicly accessible database will your **study be registered**?

[5] ICH E8 NOTE FOR GUIDANCE ON GENERAL CONSIDERATIONS FOR CLINICAL TRIALS

39. 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. How will you disseminate research findings to relevant parties, including policy makers? Describe your plan to publish your **raw, most granular study data and associated analysis 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 **data-sharing.**

OTHER REFERENCES:

See also

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

APPENDIX 1

2020 DAC best practices for informativeness

What are they?

Clinical study approaches that can make all clinical studies more likely to end informatively.

Why are they important?

- Implementation increases likelihood of informative results
- Framework to help facilitate dialogue across stakeholders and bring focus to high impact areas of the DAC Assessment Tool

#	Type	Best Practices for Informativeness
1	Design	Prioritize disease burden and epidemiology as criteria for study site selection
2	Design	Use accepted and validated endpoints whenever possible
3	Design	Proactively map study outcome to immediate or ultimate policy impact
4	Design	Rigorously justify effect estimates and prevalence assumptions
5	Design	Simulate trial to ensure right sample size and optimal design
6	Design	When feasible and relevant, apply adaptive, pragmatic, platform, or other innovative clinical trial designs
7	Analyze	Analyze real world evidence to optimize study investments, objectives, and feasibility
8	Analyze	Prior to study initiation, complete a prospective, fixed statistical analysis plan
9	Analyze	Design interim analyses with decision rules for stopping for success or futility early enough to reduce the number of participants subjected to ineffective interventions
10	Analyze	When appropriate, use model-informed drug development, such as PK/PD modeling
11	Analyze	Adhere to appropriate standards of good clinical practice, including a focus on monitoring participant safety and study integrity
12	Analyze	Use staff with experience in the therapeutic area being studied
13	Analyze	Implement a real-time data analysis capability, toward improved monitoring of recruitment targets, data quality, and other metrics
14	Communicate	Engage local regulators, ethics committees and policymakers before, during, and after the study, for input on design, obtaining relevant approvals, and action at study's end
15	Communicate	Implement a communication plan and informed consent that involves participants, families, communities, and health systems
16	Communicate	Publish protocol, analysis plan, and study results, including raw study data and code, in an open access resource, regardless of study outcome