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DAC Assessment Tool

Design, Analyze, Communicate (DAC)

A questionnaire to support the scientific design review of clinical trial study synopses and protocols to enhance the probability of an informative outcome

Version 2023

Introduction

Clinical studies are significant investments. They are a major source of information for go/no-go decisions, regulatory approval, health economics and outcomes research, policy determinations, and ultimately patient access and public health benefits. Unfortunately, too few clinical studies provide meaningfully robust answers to the questions being addressed¹. Inadequate planning of trial design, analysis and communication can lead to erroneous or meaningless results – deemed “uninformative” by some. “Uninformativeness” is detrimental to the research field because it wastes scarce resources, risks rejecting medicines or strategies that could have impact, and can erode trust between investigators and participants².

In contrast, “informativeness is a characterization of a clinical trial that indicates the study will achieve its recruitment, statistical power, and other design goals, resulting in credibly answering its research questions”³.

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

The mission of the Bill & Melinda Gates Foundation’s (BMGF’s) Design, Analyze, Communicate (DAC) Program is to improve the informativeness of BMGF-funded global health clinical studies by performing scientific design reviews, also called “DAC Reviews.” DAC Reviews are conducted by teams of BMGF-funded clinical trial experts in the areas listed above. The review approach prioritizes an overall assessment of trial informativeness, as defined by 16 validated research methods for informative clinical trial planning, or “best practices” (see Table 1 below). In addition, the review approach evaluates studies for other key critical factors. BMGF grantees that go through a DAC Review receive written feedback about their study planning that they can use to help finalize their trial protocol and other key study documents.

About this document

The DAC Assessment Tool (DAT) document is a questionnaire developed by the BMGF DAC team and filled out by grantees that go through the DAC review process. Besides serving as a key document for DAC reviews, the DAT questionnaire can also be used more broadly by Principal Investigators and their teams as a guide for informative clinical study planning.

¹ Hutchinson et al., “The proportion of randomized controlled trials that inform clinical practice” (2022) <https://doi.org/10.7554/eLife.79491>

² Zarin et al., “Harms From Uninformative Clinical Trials” (2019) [doi:10.1001/jama.2019.9892](https://doi.org/10.1001/jama.2019.9892)

³ Dolley et al., “A Maturity Model for the Scientific Review of Clinical Trial Designs and Their Informativeness” Preprints 2023, 2023040147. <https://doi.org/10.20944/preprints202304.0147.v1>

The DAT is divided into three sections of clinical study planning topics: general, design, analyze, and communicate. The DAT questions that focus on study planning details related to one or more of the 16 best practices for study informativeness are noted with a number in brackets that corresponds to the specific best practice(s) as listed in Table 1 (please note, there are DAT questions below that cite no, one or multiple best practices).

Table 1. Best practice research methods for informative clinical trial planning

<i>DAC Best Practices (BP) Definitions</i>	
1. Prioritize disease burden and epidemiology as criteria for study site selection	9. Design interim analyses with decision rules for stopping for success or futility early enough to reduce the number of participants subjected to ineffective interventions
2. Use accepted and validated endpoints whenever possible	10. When appropriate, use model-informed drug development, such as PK/PD modeling
3. Proactively map study outcome to immediate or ultimate policy impact	11. Adhere to appropriate standards of randomization, blinding, allocation concealment, and reducing bias
4. Rigorously justify effect estimates and prevalence assumptions	12. Use staff with experience in the therapeutic area being studied
5. Simulate trial to ensure right sample size and optimal design	13. Implement a real-time data analysis capability, toward improved monitoring of recruitment targets, data quality, and other metrics
6. When feasible and relevant, apply adaptive, pragmatic, platform, or other innovative clinical trial designs	14. 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
7. Analyze real world evidence to optimize study investments, objectives, and feasibility	15. Implement a communication plan and informed consent that involves participants, families, communities, and health systems
8. Prior to study initiation, complete a prospective, fixed statistical analysis plan	16. Publish protocol, analysis plan, and study results, including raw study data and code, in an open access resource, regardless of study outcome

GENERAL ASPECTS

- G1 What is the **category** of the study? *[Select from: Regulated medicine (drugs and vaccines), Non-regulated interventions (foods, implementation research), Vector control, Other – please specify]*
- G2 What is the **stage** of the study? *[Select from: Phase I, Phase II, Phase III, Phase IV, Observational, Device or Behavioral Intervention, Other – please specify]*
- G3 What is the **purpose** of the study? *[Check all that apply: drug discovery, regulatory pathway/approval, new application or extension of existing license, non-regulatory product intervention, health technology assessment, policy change, health system strengthening, Other – please specify]* [BP 3]
- G4 What is the general goal of the study and the specific **scientific question(s)** to be answered? Explain why the intervention was chosen and how the study will clearly answer or better inform the scientific question(s). [BP 3]
- G5 Outline how the proposed study fits into the overall **development or life cycle strategy** for the intervention. How will this study build on the **existing knowledge** base, what new information will it provide, and by when is this information required for most impactful informativeness? [BP 3]
- G6 What **decision, clinical program advancement, policy or policy change**, would a positive outcome in your study help to support? How will the results be generalizable to multiple countries or regions? [BP 3]
- G7 Describe how you have considered the designs and outcomes of **previous studies** and/or **real world evidence** in the design of this study (please include references). If any of these studies were of poor design or had other weaknesses, explain how you plan to address these aspects in your design. [BP 7]
- G8 Please detail the **external (to your organization) advice** you have received or plan to seek in the design of this study, including regulatory, scientific, ethical, and implementation aspects. If the study is aimed towards a change in health policy, have you engaged with policy makers to factor their requirements or concerns into the design of this study? Have you solicited or received advice from local experts regarding epidemiology, existing interventions, relevant standards of care, and conduct of studies in the setting you propose? If so, please describe. [BPs 1, 3, 14]

- G9 Describe your plans for **study monitoring**, ensuring data integrity and quality management. [BP 13]
- G10 Describe what you or others see as the **limitations, challenges, and risks** of this proposed study. Please summarize your mitigation plans for each.

DESIGN ASPECTS

- D1 Describe your rationale for the proposed **study location(s)** including disease burden, availability of disease-specific trained staff and facilities, and assumptions used for expected site recruitment rates. How recent and localized are your prevalence estimates? [BPs 1, 4, 12]
- D2 Describe how the **duration** of the study is adequate to answer the scientific question(s), considering the anticipated clinical efficacy effect, as well as expected duration of effect and risk of treatment failure or relapse. [BP 4]
- D3 Detail the main potential sources of **bias** during the study and how these will be minimized. [BP 11]
- D4 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. [BP 11]
- D5 Please describe your plans for **blinding** the study. Please describe who will and will not be blinded to study treatment (e.g., data monitoring committee, steering committee), and plans for blinding/unblinding study data during the analysis phase of the study. [BP 11]
- D6 Describe your **safety** monitoring plan including any safety aspects that require specific monitoring and/or mitigation action. How will safety alerts be handled? [BP 13]
- D7 Describe how the proposed **eligibility criteria** relate to the population suffering from, or at risk of, the disease or condition. If this is a cluster randomized trial, what eligibility criteria will apply to clusters? [BP 1]
- D8 What steps will you take to ensure a population as **diverse and representative** as possible and appropriate will be included in this study?
- D9 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. [BP 3]
- D10 Will the effects of **biological sex** on pharmacokinetic/pharmacodynamic (PK/PD), efficacy, and/or safety be investigated in the study? If so, how, and if

not, why not? If both biological sexes are eligible for enrollment, are measures needed to ensure both have equal opportunity to enroll?

- D11 Will this study enroll **special populations** (e.g., elderly, children, pregnant women, nursing mothers, HIV-positive individuals)? Describe any special safety considerations needed to enroll these populations. Is the target population for clinical use likely to include these groups? 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. [BPs 3, 13]

References: https://database.ich.org/sites/default/files/E7_Guideline.pdf

https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf

- D12 How do the **primary and secondary endpoints** address the scientific question(s) and purpose(s) of the trial? Please describe or reference the general acceptability of your selected primary and secondary endpoint methodologies. If no validated or 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 informativeness of this study. [BPs 2, 14]
- D13 Please describe the rationale for the selection of the **time period for measuring the endpoints**. Also describe what is known about the variability of your selected primary and secondary endpoints. For example, consider diurnal variability, seasonal and geographic variability, measurement variability, intra-person variability and spatial variability (if cluster-randomized). [BP 2]
- D14 What are the **strengths and limitations of these endpoints** regarding the consistency with which they may be ascertained in study subjects? [BP 2]
- D15 For endpoints that are based on lab data that are non-routine (e.g., antibody titers and other biologic assays), and collected at multiple lab locations, please describe how the **endpoint assays** are validated across the different labs. [BP 2]
- D16 What is the basis for the **effect size** estimate used to power your study? Is the study powered to detect the minimally clinically relevant effect size? Describe the current data or assumptions that justify the response rates and explain if and how it varies depending on the severity of the disease. [BP 4]
- D17 What is the basis for the **sample size** calculation? Did you use simulation to perform your sample size calculation, and if not, would you be willing to? [BP 5]
- D18 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? If you are not presently committed to one, please comment on how a pilot or run-in period might be a beneficial addition to correct for or improve inputs on actual site-

specific burden of disease, recruitment rates, and other potential inputs. [BPs 4, 13]

- D19 Provide a detailed description of the **simulations** that were conducted as a part of developing your proposed study design and sample size, 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 simulations were not run, please explain the rationale why not. [BP 5]

For regulated medicines only:

- D20 Describe the **dose selection** criteria. Please provide background documentation related to model-informed drug development considerations including PK/PD assessments, exposure-response modeling, dose ranging studies, or regimen/dosing frequency studies that support the dose and regimen selection. Are there any demographic factors (age, sex, body weight, race) that may influence exposure to the intervention? Have you performed or will you perform modeling considered model-informed drug development for this trial? [BP 10]
- D21 Is the drug or vaccine or product under test currently licensed and being used in accordance with the **license and/or standard of care**? If not, do you anticipate any changes before further studies?
- D22 Describe your plans for **PK (and, if applicable, PD/biomarker) sampling** during this study. How will results be compared to what is already known about the disposition of the test medicinal product? How will PK data and parameters be linked with PD effect, efficacy measures, and/or adverse events? [BP 10]

For regulated medicines or non-regulated interventions only:

- D23 Explain how the potential for **PK or PD 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 and inclusion/exclusion criteria. [BP 10]

For vector control studies only:

- D24 Are there plans to monitor **environmental impact** and minimize any impact? How will interventions be disposed of at the end of the study?
- D25 Are there plans to monitor **durability and efficacy** over the life of the product? Please explain the rationale to monitor or not.

ANALYZE ASPECTS

- A1 Describe your **statistical analysis plan**, including 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. Please also describe your plans to analyze and report disaggregated data by biological sex, including data for withdrawals or dropouts. [BP 8]
- Reference: Stevens G, Dolley S, Mogg R, Connor JT. A template for the authoring of statistical analysis plans. Contemp Clin Trials Commun. 2023 Jun 9;34:101100. doi: 10.1016/j.conctc.2023.101100*
- A2 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. [BPs 6, 9]
- A3 Describe how **adherence** with treatment is being measured and analyzed. What is known about adherence with the intervention in this patient population? Are there sex considerations in adherence?
- A4 Describe your **data collection and management plan**. Are you planning to include real-time data collection and analysis tools? If so, provide details. Are you planning to use digital data collection tools? If so, have they been appropriately validated and certified? [BP 13]

COMMUNICATE ASPECTS

- C1 Describe your **community engagement** strategy and communication plan, including timing. Do you have a communication plan for how you will promote and communicate the trial toward optimizing recruitment? How could you do more? [BP 15]
- Reference: Shelly, C.E., Logan, C., Skorochood, B. et al. Creating a best practice template for participant communication plans in global health clinical studies. Trials 24, 158 (2023). <https://doi.org/10.1186/s13063-023-07185-4>*
- C2 Describe your plans for **study consent** (or alternatively community assent), including allowing data reuse and biological sampling. [BP 15]
- C3 If a multi-site study, please describe your **cross-site communication and collaboration plan** that ensures alignment of study site protocols, clinic operations training, data collection, data standardization, and cross-site data sharing. [BP 15]

C4 On which publicly accessible **database** will your study be registered? *[Select all that apply: ISRCTN, clinicaltrials.gov, Pan-African Clinical Trials Registry, Other please specify]* [BP 16]

Note: It would be expected that registration would be on one of the WHO compliant registries or clinicaltrials.gov

C5 Describe your commitment and plans to **publish** study results in an open access journal as soon as is practical, regardless of outcome, as well as your forecast of when the publication will be submitted following database lock. [BP 16]

C6 How will you **disseminate** research findings to relevant parties, including policy makers? [BP 14]

C7 Describe how you will facilitate data sharing of your study results including 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. [BP 16]