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Protocol Evaluation Questions

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Many a research site has embarked on a clinical trial only to discover, too late, that it will be far more difficult than initially expected. The questions in Figure 1 can help sites determine the feasibility of clinical trials. Problematic studies can be avoided, more generous budgets can be negotiated, and steps taken to maximize the chances of success. On the other hand, attractive studies can be prioritized. The long list of questions below speaks to the complexity of clinical trials. Although most of the questions may be innocuous for a specific clinical trial, it takes only one negative answer to doom a study to failure. Organizations must often make business decisions based on incomplete information. However, if the answer to any question is unknown, an unfortunate answer may eventually emerge. If the questions cannot be answered expeditiously, "paralysis by analysis" creates its own problems.

Many of the questions can lead to further questions. For example, if the answer to question 12 – "What is the comparator?" – is "placebo," it becomes necessary to evaluate the standard-of-care implications and likely affect on subject recruiting, adherence and retention. If the comparator is a marketed drug, the dosage of that drug must be evaluated vis-à-vis standard of care. The comparator may create its own set of adverse events.

Answers to many questions can be found in the protocol, investigator's brochure, and informed consent form. The study sponsor/CRO can answer some questions. Friendly sites may have useful information. Answering other questions will require experience, which can be gained only by conducting studies without complete information.

Experienced sites have learned that study sponsors often do not think through the issues raised by these questions. Although the questions are written from the research site's perspective, study sponsors and contract research organizations (CROs) can use them to anticipate potential problems that a study, or specific site, may experience. Sponsors and CROs should discuss the questions in some detail during the protocol design process with a panel of potential investigators, and not just the key opinion leaders. Summarizing the answers for potential sites can speed their feasibility analysis. Concealing potential problems may help recruit sites, but with dire consequences once they discover the truth midway through the study.

The questions below are grouped in categories, but many of them have implications for multiple categories. Some questions are more important than others and should be answered first to weed out unlikely studies.

Figure 1. Protocol Evaluation Questions

Study design and objectives

1. Is the protocol title clear and accurate?
2. Is this the final version of the protocol?
3. Does the protocol reflect competent preparation?
4. Are the objectives, rationale and activities of the study clearly stated and sensible?
5. Is the study justified by its scientific objectives?

6. Is this study similar to previous studies we have conducted, and what were the results of those studies?
7. What phase is the study?
8. Are prohibited activities required before informed consent is obtained?
9. Can all activities scheduled for each visit be completed in that visit?
10. What are the safety and efficacy endpoints for the study, and how are they measured?

Treatment

11. What is the study drug?
12. What is the comparator?
13. What is the ratio of subjects per arm?
14. How does study treatment differ from standard of care?
15. Is there a problematic washout period?
16. Are there technically difficult treatments, procedures or assessments?

Study schedule

17. Is the schedule reasonable and practical?
18. When will we initiate the study and how does that date compare to other sites?
19. What is the enrollment period?
20. What is the follow-up period?
21. Will visits be performed outside normal business hours or create logistical challenges?
22. How often will the study be monitored and how will monitoring be conducted?
23. Are there any interim milestones, e.g., for data submission?

Subject protection

24. What are the benefits, risks and burdens for the subjects?
25. Is the use of a placebo, if any, acceptable?
26. Does the study raise any standard-of-care issues?
27. Is the safety profile of the study drug acceptable?
28. Are there any other subject protection or ethical issues?
29. Will the IRB have issues?

Subject recruitment and retention?

30. Are the enrollment objectives – numbers and time period – realistic?
31. Do we have access to the study population?
32. Where and how will we find potential subjects?
33. Will they be interested in participating?
34. Is the study duration very long?
35. Are the visit schedule and times acceptable for subjects and practical for study personnel?
36. How much flexibility is there in visit dates?
37. Are there frequent, inconvenient or unpleasant procedures?
38. Is the dosing schedule inconvenient or complex?
39. Are subject diaries required?

40. Are the eligibility criteria too strict?
41. Are the eligibility criteria clear and unambiguous?
42. Are the screening procedures practical, limits and yields reasonable, and payments acceptable?
43. Are there seasonal issues?
44. Do we, or will we, have other studies competing for the same subjects?
45. Are other sites in the local area participating in the study?
46. Is enrollment competitive?
47. Are subjects from populations with extra recruiting and informed consent requirements?
48. When do subjects become evaluable?
49. Are subjects likely to stay in the study for its duration?
50. What subject recruiting support will the sponsor provide?
51. What costs will subjects incur?
52. What subject compensation makes sense?
53. After completion of the study, how and when can subjects get access to the study drug?

Adverse events

54. How many AEs and SAEs should we expect?
55. What types of adverse events are recorded or reported?
56. What are the known side effects of the study drug?
57. What are the implications of pre-existing medical conditions for classifying adverse events?
58. How is the randomization code broken?
59. Who pays for treating subject injuries?

Personnel

60. Do we have qualified personnel available to conduct the study?
61. Does the study require above-normal time to conduct, e.g., visit lengths or CRF pages?
62. Is additional staff training required?
63. Are there unusual pharmacy, dispensing or accountability requirements?
64. Is specialist expertise required, e.g., for assessments?
65. Can the principal investigator delegate activities normally?
66. Are there any limitations on subinvestigators or satellite sites?

Facilities and equipment

67. Do we have access to required facilities and equipment?
68. Are the laboratories local or central?
69. Are the arrangements for shipping lab specimens practical?
70. Are laboratory tests required when the laboratory is closed?
71. Do laboratory and other facilities have adequate capacity?
72. Do we have adequate space and equipment to store study materials and records?

Other

73. Do we have previous experience with or references for the sponsor?

74. Do we have previous experience with or references for the CRO?
75. Do we have ready access to sponsor/CRO personnel?
76. Does the study budget support our financial and other objectives, such as patient care, education, physician relations, and marketing?
77. Is the study sponsor financially sound?
78. Are there third-party payor reimbursement issues?
79. Does the clinical trial agreement include problematic terms?
80. What study activities require pre-approval by the sponsor (e.g., unscheduled visits, extra lab tests, subject injury treatment, and advertising)?
81. Will EDC/eCRF be used?
82. Are there unusual requirements as to how study activities are performed?
83. Are there unusual reporting or other administrative requirements?

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