Outline for Performing NDA Review

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Objectives of the Review

- ***Verify accuracy of the data***
- ***Verify accuracy of the efficacy claims***
- ***Verify accuracy of the safety claims***
- ***Place the efficacy claims in the context of accepted practice***
- ***As part of verifying accuracy, look for hidden, false, or misleading data (usually based on feelings and impressions during the review process, which then lead to specific database queries to confirm or refute initial impressions)***

INITIAL ORGANIZATION

When the NDA arrives, unpack and shelve *all* volumes.

Find all disks and load database on computer.

Skim briefly to be sure there is reviewable data (i.e., refuse to file evaluation).

Leaf through table of contents and volumes.

Start a "Key Volumes" list.

Write a "Material Submitted" section describing what material is available for review.

Determine how many trials have been submitted.

Identify trials essential for approval and supportive trials.

Identify peripheral supportive trials.

Determine which trials will require DSI audit; how many centers; which centers.

Generate audit sheets with team leader.

Talk with DSI.

Brief Summary from Non-clinical Disciplines

Utilizing the Applicant's summary documents, write a brief summary of data from the following disciplines:

* Chemistry (CMC)

* Animal pharmacology / toxicology

* Human PK/PD

Include issues that might be clinically relevant (isomerization, active metabolites, dose trial formulation versus to be marketed formulation, potential for drug-drug interactions, etc.)

REGULATORY REVIEW

NOTE: these steps may be performed prior to NDA submission if you are notified in advance.

If possible, find out in advance which NDA you will be reviewing

Copy NDA template, name it, fill in available blanks (sponsor, drug name, etc.)

Do literature search. Request relevant and required documents from the library.

If the drug is an NME, look at relevant published literature.

If the drug is established, limit search to the relevant stage and type of cancer.

Write "Relevant Human Experience / Literature Review" section.

Get the division files, the pre-NDA package, and the pre-NDA meeting minutes.

Review division files, pre-NDA package, and pre-NDA meeting minutes.

Identify possible problems with the application, or issues identified by FDA.

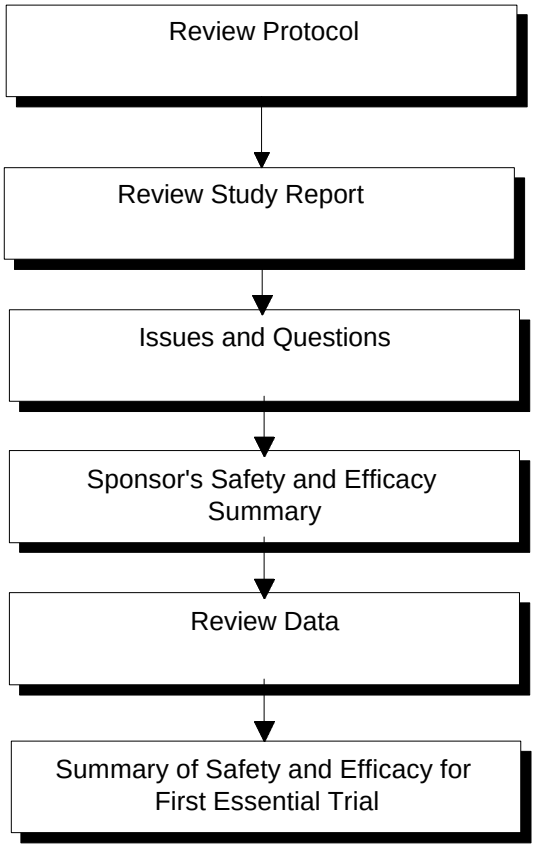
Write a "Regulatory History" section.

Make a list of contentious issues or areas that need attention.

Consider a divisional search for related INDs; may or may not be relevant.

Determine what drugs have same labeled indication and summarize in review document.

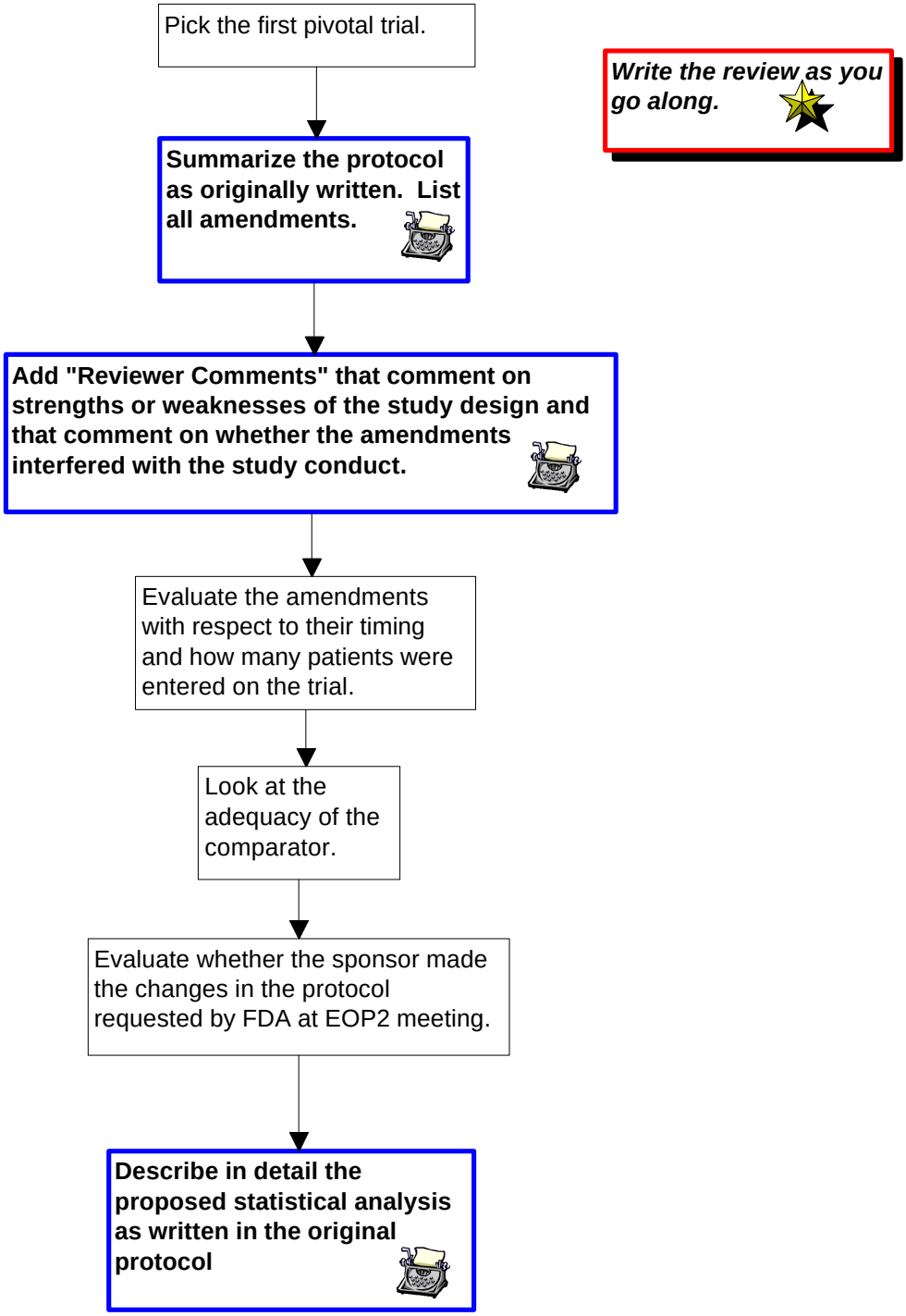
Review First Essential Trial



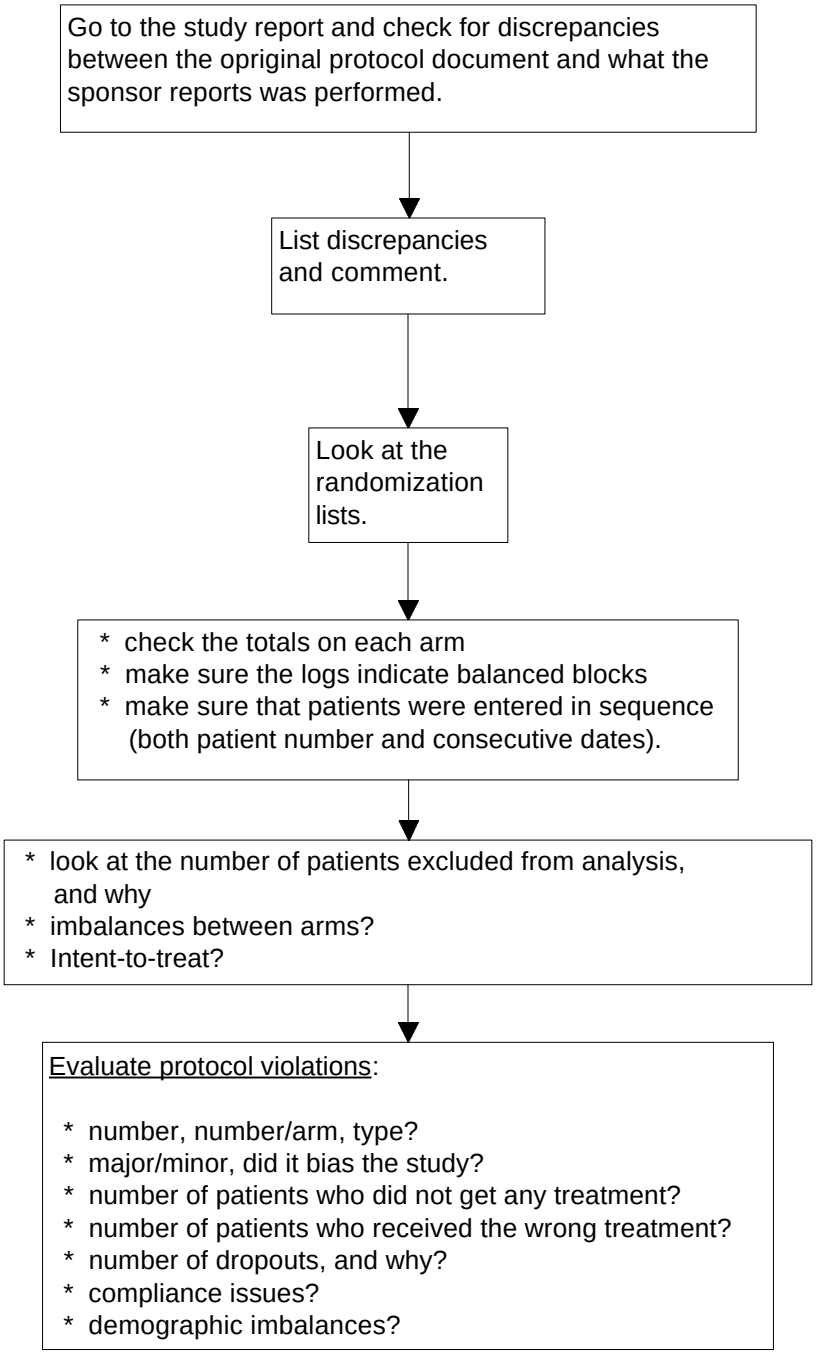
Clinical-Statistical Interactions p 8.0

Review tips and other issues p. 9.1-9.2

First Essential Trial - Review Protocol



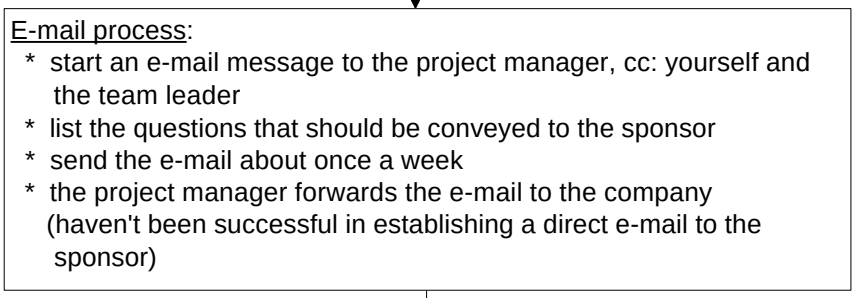
First Essential Trial - Review Study Report

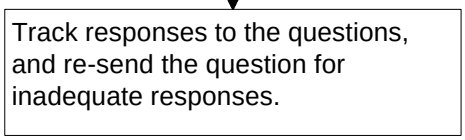


First Essential Trial - Issues and Questions

Keep a paper copyof the list of issues and questions on your desk for reference.

List issues and questions to be resolved.





This process continues during the entire review.

First Essential Trial - Sponsor's Safety & Efficacy Summary

Keep a running list of Reviewer Comments throughout the document, and a paper copy of any questions incorporated in these comments. Ask yourself - what seems wrong?

Use the study report to summarize what the sponsor concluded about efficacy, then repeat for safety.

Look at EOP2 and pre-NDA meeting minutes and determine:

* Do the analyses match those in the original protocol?

* Do they match those recommended in the meeting minutes?

First Essential Trial - Review Data

Go to the data. Look through the tables. Look carefully through any column in a table marked "Other" (it's a good place to hide information).

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Start doing queries. Start with simple ones - cross-checking a safety issue, checking age, etc.

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Develop a series of queries designed to check the primary endpoints - begin with the most crucial endpoint (i.e., do survival before tackling response).

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Evaluate safety issues. Read all mortality narratives.

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Additional queries will be suggested by initial results, and by reading the study report with a critical eye.

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Results should be written as Reviewer Comments - do the queries agree with the sponsor's conclusions? What are the differences?

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Move on to difficult queries - response and TTP.

First Essential Trial - Summary of Safety & Efficacy

Write a summary of safety and efficacy for the study. It should include:

* whether the analyses are appropriate and previously agreed upon

* QOL - quality of the data

* QOL - whether the differences are clinically relevant as well as statistically significant

Other Clinical Trials & Non-Clinical Issues

Repeat the process used for the first essential trial with all essential trials and key supportive trials.

Write a summary of the supportive trials.

Pick out the issues that may be clinically relevant:

* the medication needs to be taken with food
* how might non-compliance affect study results?
* are there drug-drug interactions that will be important?
* does the drug need to be refrigerated?
* is the marketed drug product the same one used in the pivotal trials?
* if not, is there a bridging study?

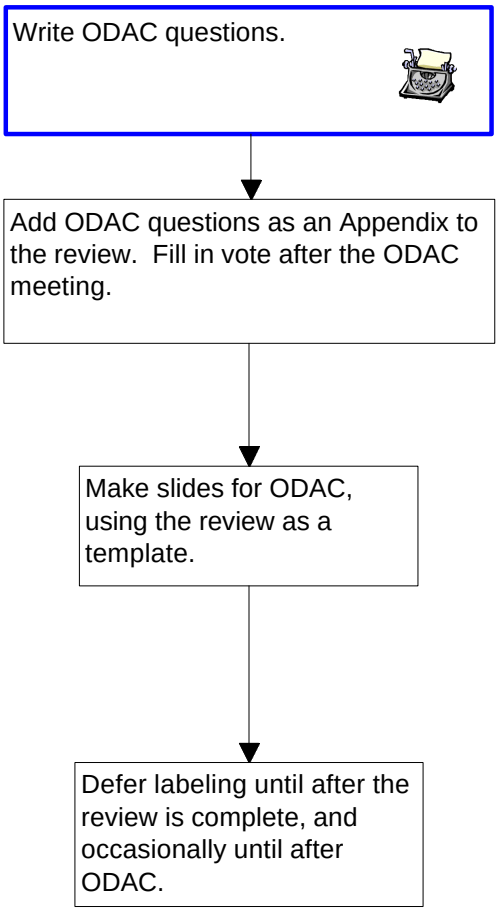
Integrated Summary of Safety and Efficacy

Summarize the sponsor's Integrated summary of safety and efficacy.

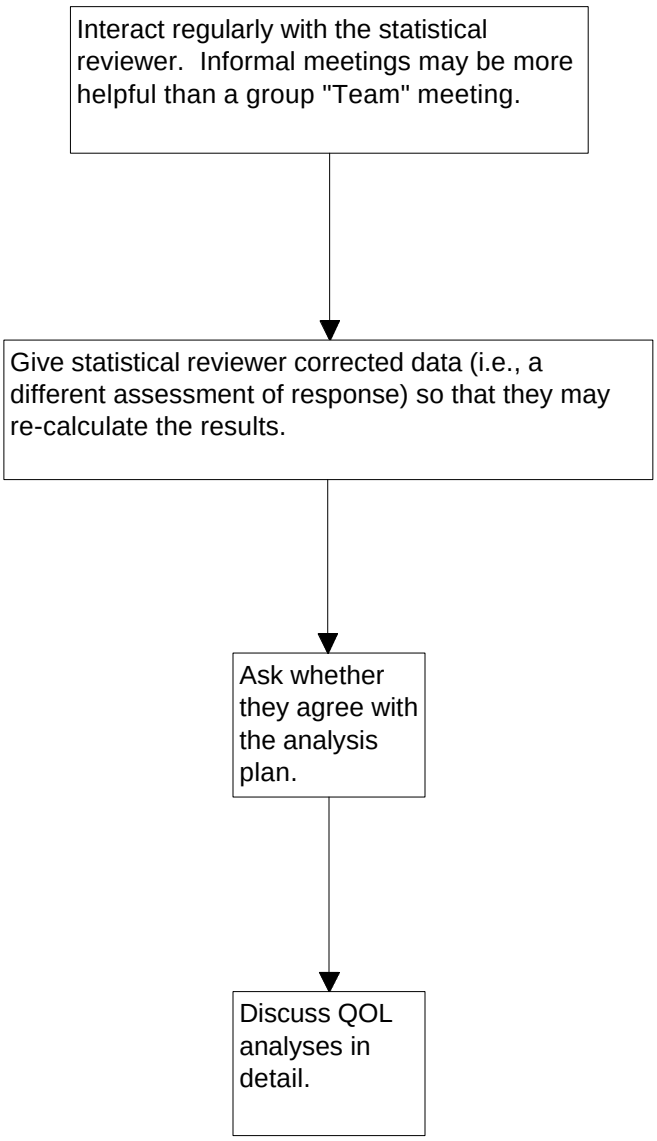
Write a reviewer's ISSE:

* indicate whether the review agrees with the results and conclusions reported by the sponsor
* indicate whether there are additional problems/issues
* do all the studies support each other? If not, why not?
* which study is "the best"?
* create a table with the sponsor's results and the FDA results side-by-side for comparison
* put the table in the context of approved drugs and clinical practice
* discuss the risk/benefit ratio
* make a recommendation regarding approval or non-approval

Oncologic Drugs Advisory Committee



Clinical-Statistical Interactions



Susan's Other Issues - #1

4-month <u>safety updates:</u> I skim them to be sure they don't contain something new. With the rapid pace of submission and review, they seldom contain relevant new information.

I leave <u>unresolved issues</u> in CAPS in my review, with a paper list on my desk. I correct these sections as answered by the sponsor.

<u>CRFs</u>: Review as needed, based on the application. For one drug, I needed to spot-check a few, as all data were electronic and reproduced from the CRFs. For another drug, I had electronic CRFs, but these were generated by the company I needed to review the CRF on every patient to verify TTP. For as third drug, CRFs were the only data provided.

Susan's Other Issues - #2

Audits: **Request DSI audit of 1-2 essential trials, or 1 essential trial if there are several indications. Choose 2-3 sites/trial, usually the highest accruers. Have DSI audit discrepant sites - significantly better or significantly worse results than the rest; sites known to DSI to have data problems. Consider requesting DSI audits of sites rarely used in clinical trials or sites with the most protocol violations. Perform reviewer audits of CRF and compare to electronic data - usually some general datapoints, and key endpoints.**

CANDA: usefulness limited by lack of uniform format among all companies. More helpful to have protocol and study report on disk, with complete electronic datasets. Electronic CRFs are very helpful.