Outline for Performing Medical Review of NDA

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Links to Resources

*Includes significant input from John Johnson, Susan Honig, Alison Martin, Greg Dubitsky, and Bob Justice.

Last Updated 4/26/99, G. Williams

Table of Contents

Objectives of the Review

- *Identify efficacy and safety claims*
- *Summarize regulatory history of this and similar NDAs*
- *Work with DSI to validate primary data*
- *Critique trial design and conduct*
- *Summarize and critique applicant's analyses*
- *Selectively verify applicant's findings*
- *Perform additional analyses utilizing primary data*
- *Summarize risks and benefits*
- *Communicate findings to advisory committee*
- *Make recommendation*
- *Document review process*

Review Tips*

Write as you go

Starting with regulatory background and then protocol, study report, and your review of the data, write the review document as you go along.

Distinguish applicant's findings and tables

Utilize quotes and tables from the study report to represent the applicant's findings. Clearly distinguish the applicant's analyses from your own, e.g., "the following table from the application(volume 7 p 22)" or "Sponsor's table x" or Reviewer's table y."

Reviewer Comments

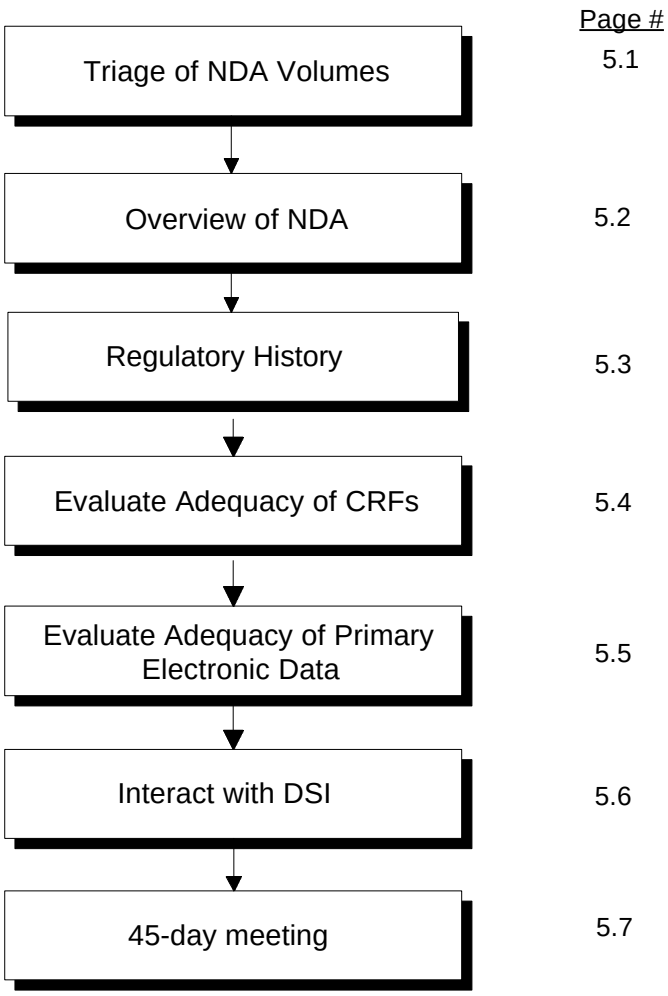
Throughout review intersperse "Reviewer Comments" that address the strengths and weaknesses of the applicant's design, conduct, or results. This helps to make a clear distinction between the applicant's and the reviewer's findings and conclusions.

List of questions

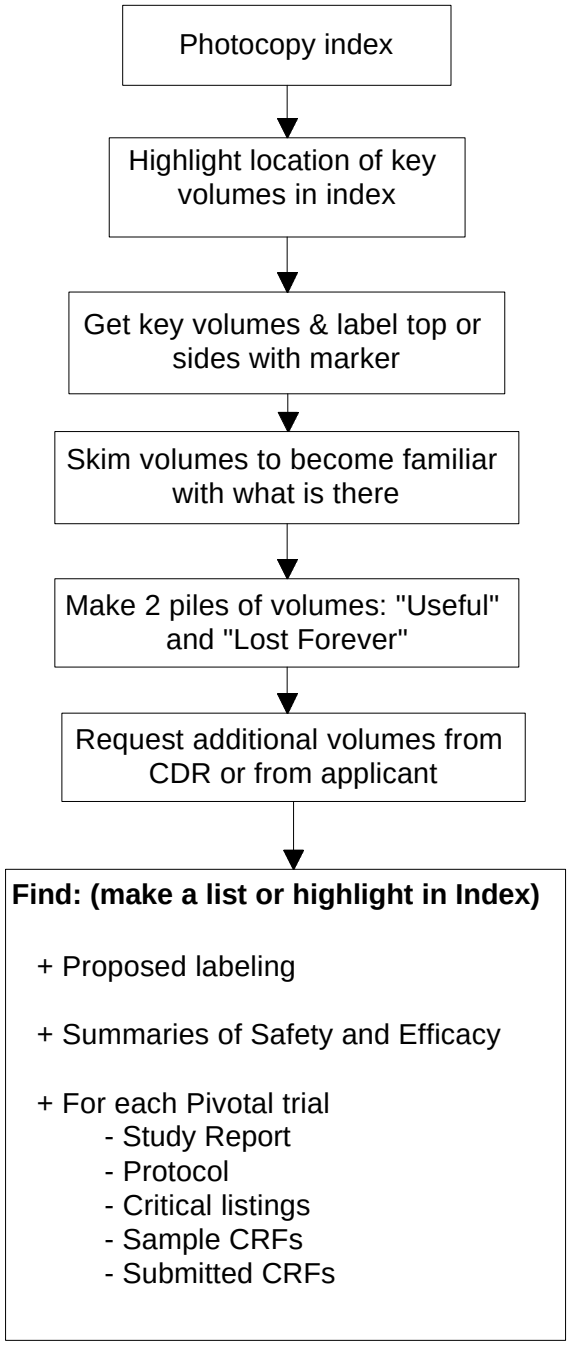
Make a list of questions and problems as you review the protocol and study report. Mark places in review that correspond to pending questions (for instance use asterisks or CAPS). Periodically send list of appropriate questions to applicant. A weekly email to the project manager may serve this function. Keep a log of questions asked and answers received. Answer other questions during your own review of the data.

*Derived from review diagram by Susan Honig

INITIAL EVALUATION OF NDA
(preparation for 45-day meeting)

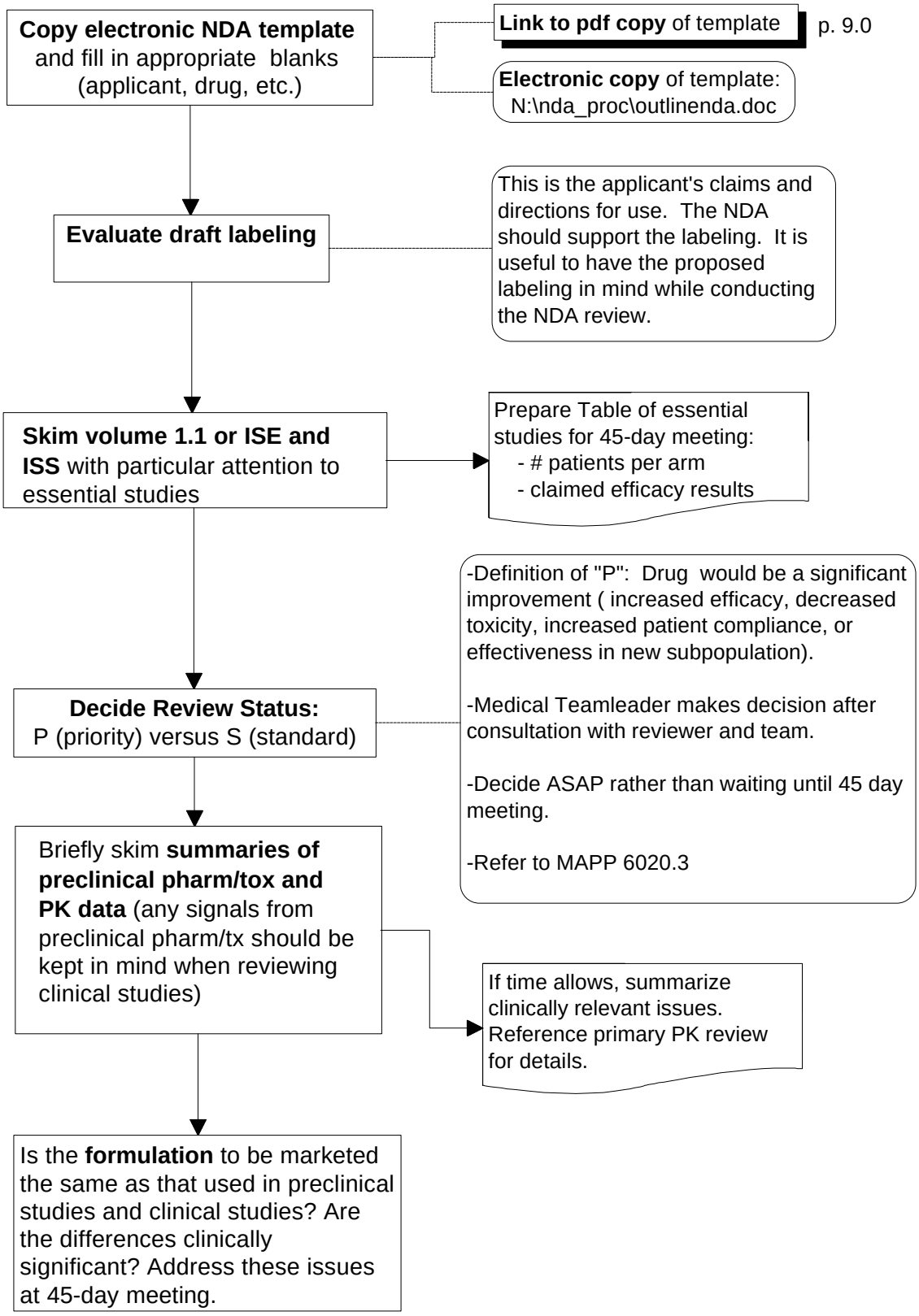


Triage of NDA Volumes*



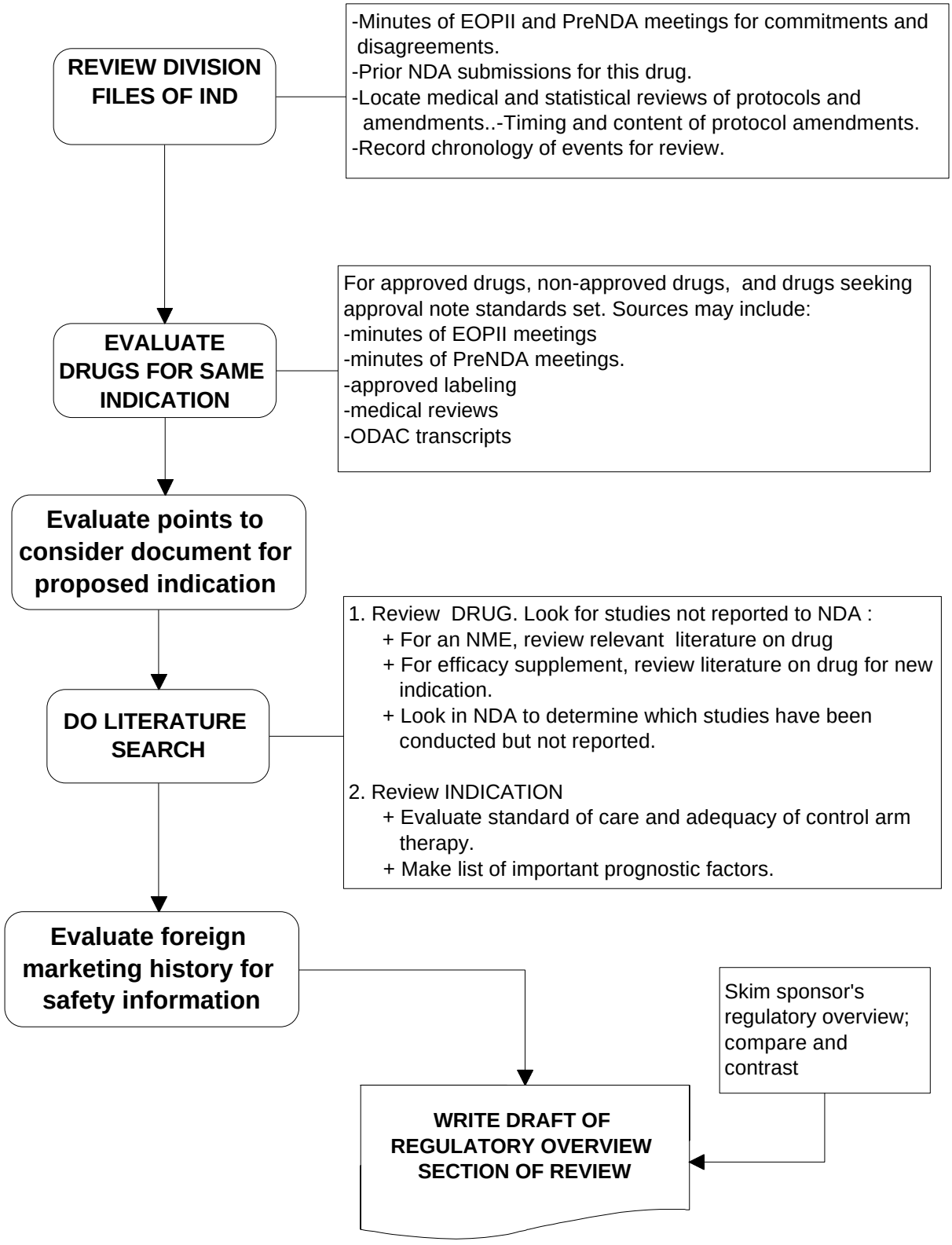
* From diagram by Anonymous reviewer

Overview of NDA

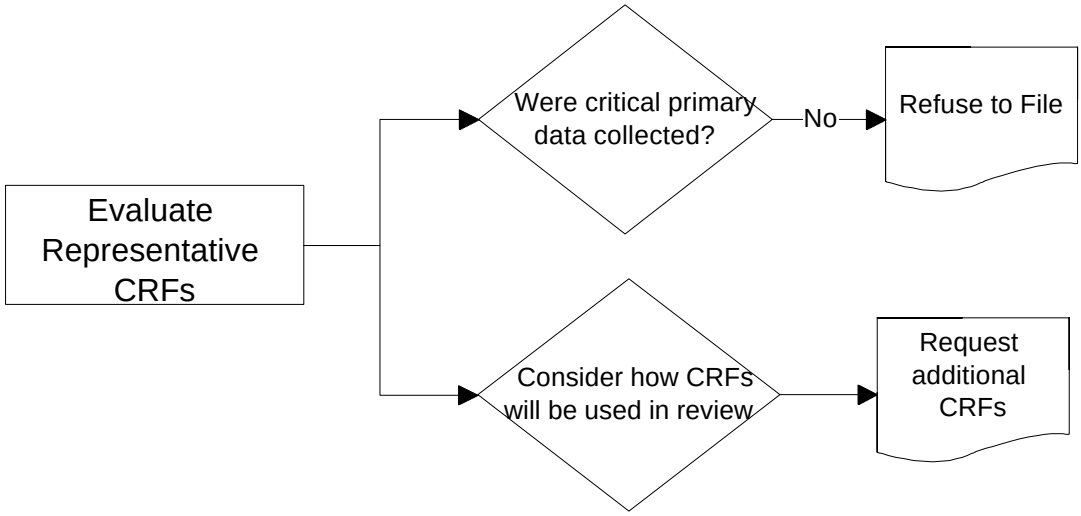


REGULATORY HISTORY

(May begin before NDA submission but may also be done later in the review)

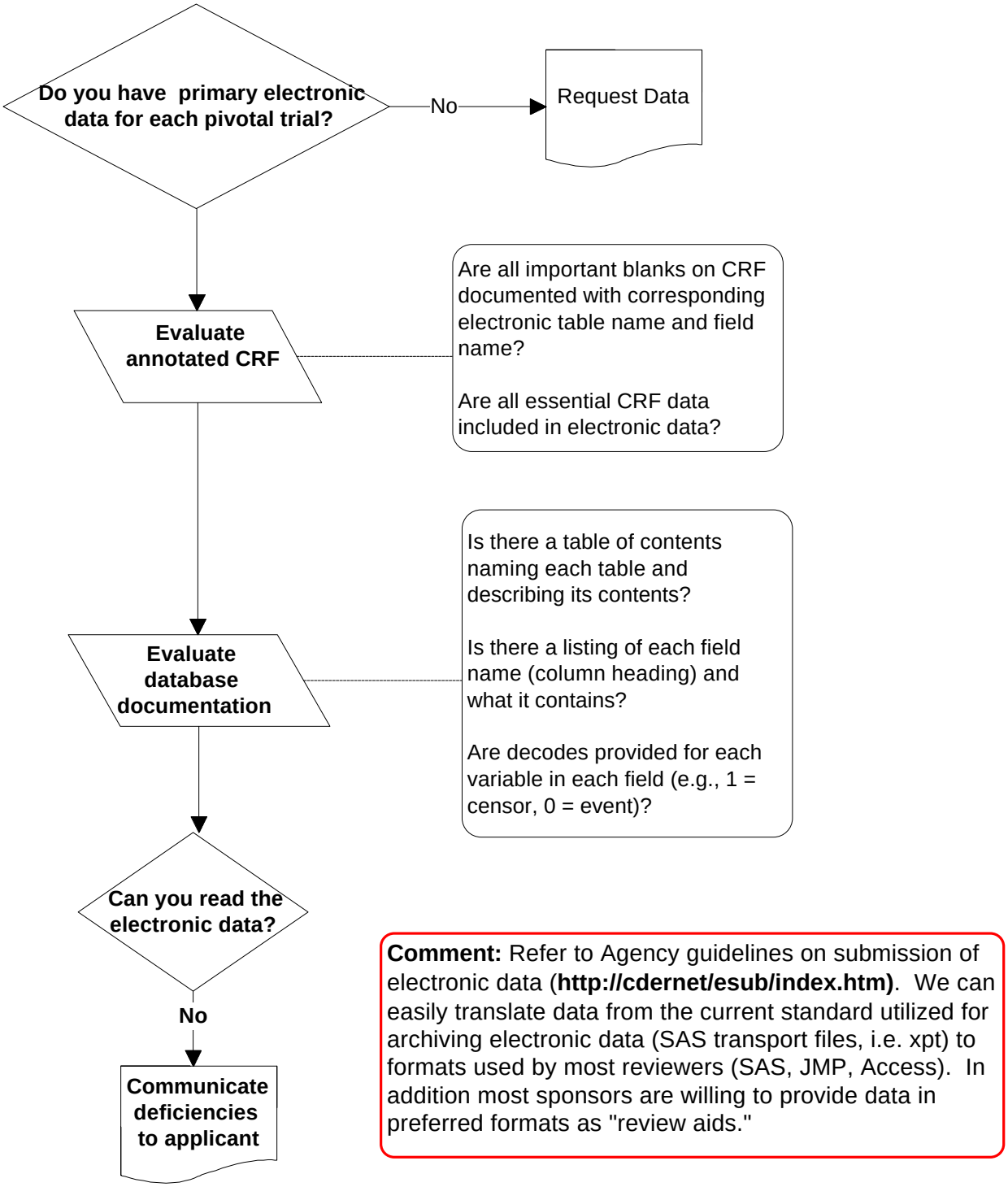


Evaluate Adequacy of Case Report Forms



Comment: Regulations require submission of CRFs for deaths and dropouts unless otherwise specified. In oncology submissions, not all deaths are relevant. We commonly request submission of CRFs only from those deaths occurring within 30 days of treatment. Additional requests are often used to select a reasonable number of more clinically relevant CRFs. For instance, every 5th responder and every 10th non-responder might be selected if one is interested in validating the response evaluation process. In small uncontrolled trials, CRFs from all responders are usually requested.

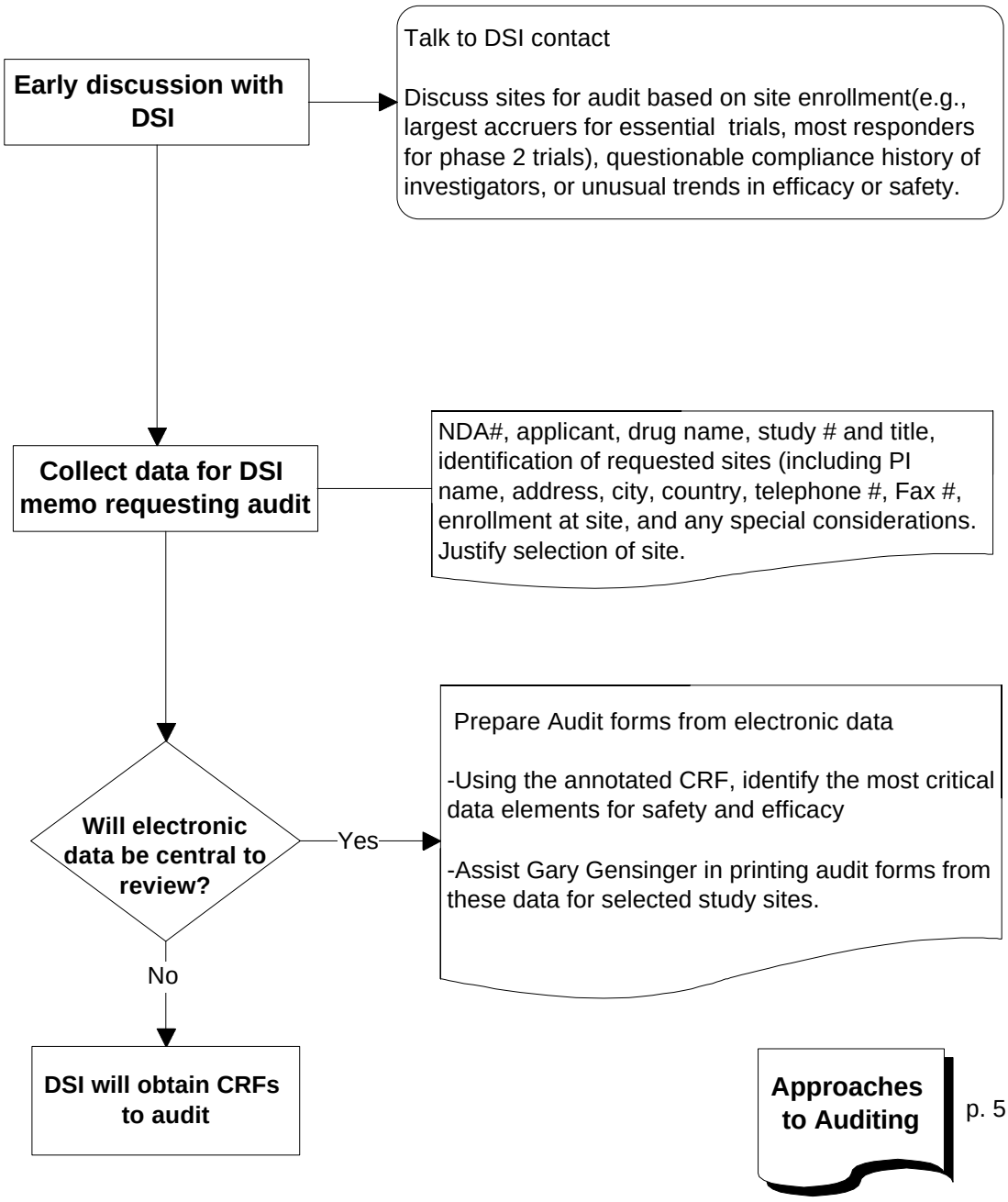
Evaluate Adequacy of Primary Electronic Data



Comment: Refer to Agency guidelines on submission of electronic data (**http://cdernet/esub/index.htm)**. We can easily translate data from the current standard utilized for archiving electronic data (SAS transport files, i.e. xpt) to formats used by most reviewers (SAS, JMP, Access). In addition most sponsors are willing to provide data in preferred formats as "review aids."

Interact with DSI

(before 45 day meeting)



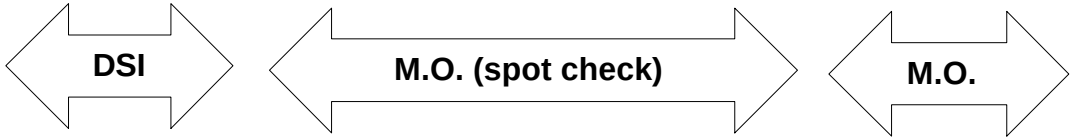
p. 5.6.1

APPROACHES TO AUDITING DATA

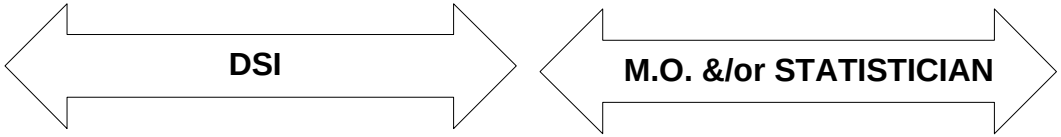
DATA FLOW

Traditional method 1:
DSI audits CRF. Medical officer reproduces analyses from CRF

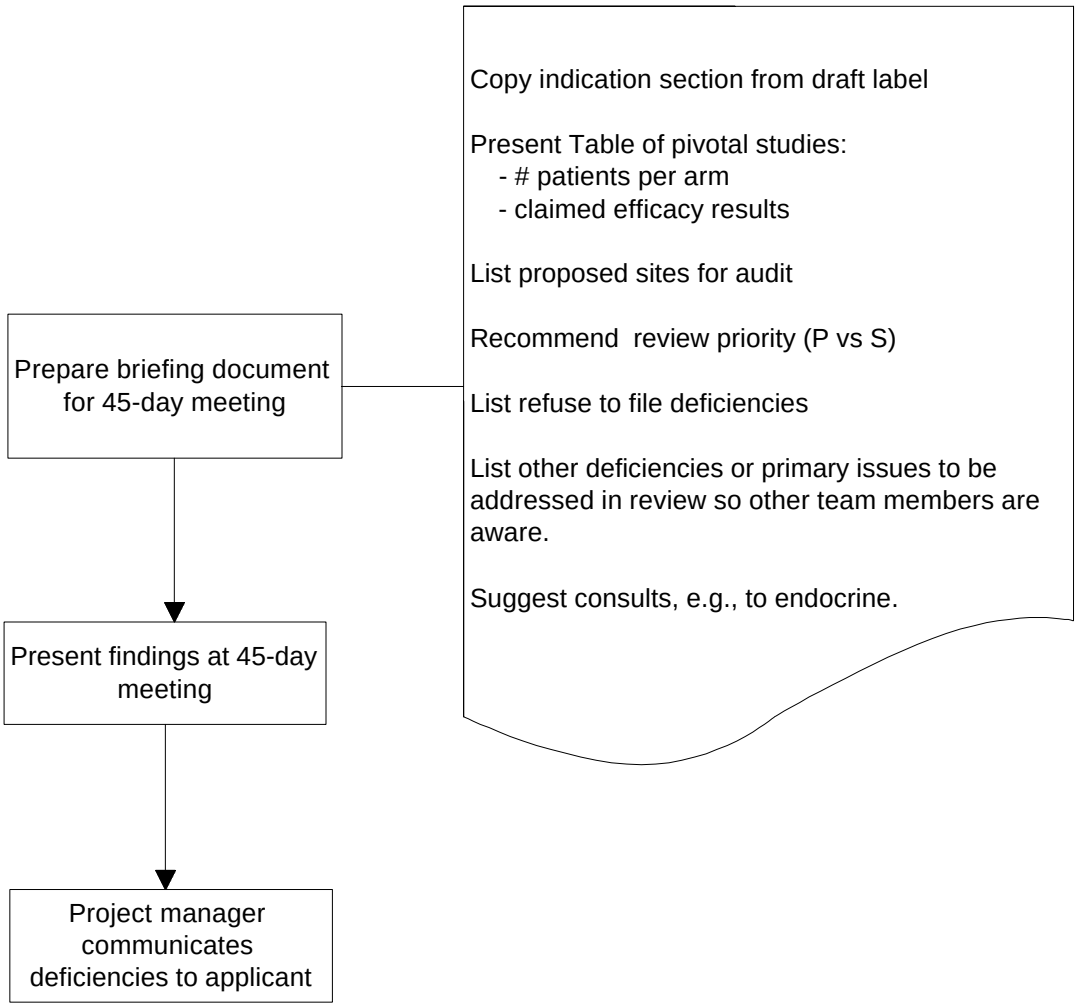
Traditional method 2:
DSI audits CRF. Medical officer reproduces analyses from listings. Medical officer spot checks listings to CRFs. Statistician utilizes unverified electronic data.



Electronic method:
Review division produces audit forms from electronic data. DSI audits electronic data. Medical officer &/or statistician reproduce analyses from electronic data.



45-day meeting



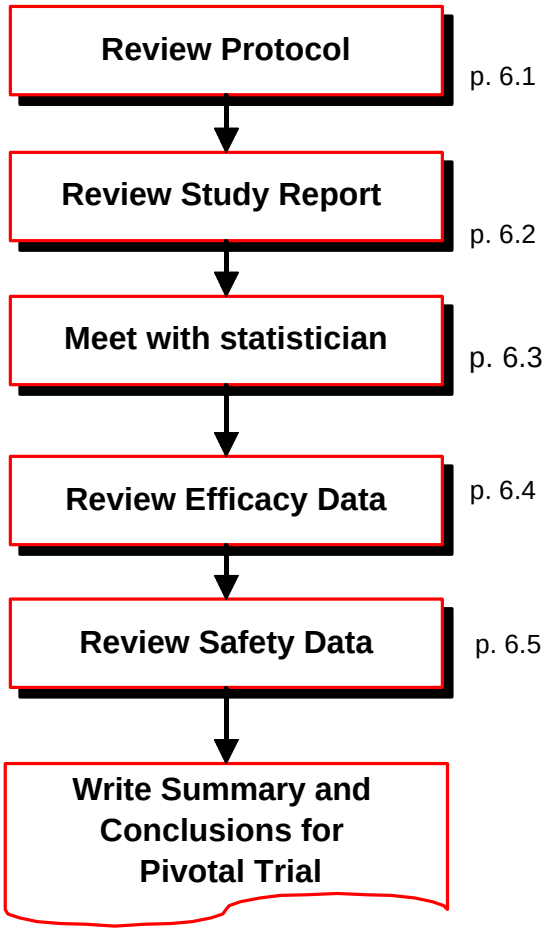
Review of pivotal trials

Introductory comment:
Ideally, the next step in review would be to evaluate the "conduct" of the study. Unfortunately, conduct of the study must be inferred from findings in the study report or in the data. Different approaches may be used for evaluating the study report, data listings, electronic data, and case report forms. The recommended approach is to first evaluate and summarize the study report, noting inconsistencies between analyses used and those specified by protocol or by agreements. If the applicant's results are not supportive of NDA approval, reviewer evaluation of efficacy data from this trial may not be necessary. Problems and questions noted during review of the study report should guide the reviewer in analyses of the data.

Note: As you proceed with review of the study report and of the data, refer to "factors to consider" pages for Conduct and for Results

Link to "Conduct" p. 6.4.2

Link to "Results" p. 6.4.3



Pivotal Trial: Review Protocol

Review the **original** Protocol and **all** protocol amendments. The applicant's description of the protocol in the study report may not be accurate. Record your summary of the most pertinent points. An exhaustive reproduction of all protocol details is not needed.

List protocol amendments

+ List date and a title for each amendment.
+ Describe significant amendments
+ For critical amendments, determine the number of patients affected. e.g., the number accrued after that date.
+ Note which amendments which were likely to alter the outcome of the study.

Consider Design

+ Describe trial design (open randomized controlled, etc.)
+ Is design adequate to achieve objectives?
+ Are objectives adequate to support approval?
+ Are there data supporting the choice of control treatment?
+ Did the applicant make changes requested by FDA at the EOP2 meeting?
+ Consider inclusion criteria versus population covered by the labeled claim.

Randomization Process

+ Is the randomization process adequately described?
+ Is randomization central or local; what are randomization strata, what are block sizes?
+ Consider how the randomization process might be validated during review or DSI audit.

Treatment

+ Describe dose, schedule, and duration.
+ Describe criteria for dose adjustment, holding, and discontinuing treatment.
+ Does the protocol provide enough detail to assure patients are treated in a uniform manner?

To page 2

Protocol Review (2)

From Page 1

Efficacy

+ Describe the primary endpoint in detail.
+ Does the primary endpoint point represent patient benefit?
+ Evaluate and record the schedule of baseline and followup tests. Is it adequate?
+ Are measures taken to minimize bias?

Safety

+Are the timing and type of safety evaluations adequate?

Statistics

Record key elements of statistical plan:

+ What is the primary endpoint according to statistical plan. (This takes precedence over other sections of protocol.)
+ What is the planned sample size. Is it adequate?
+ What is the exact analysis plan for the primary endpoint including the statistical test to be used?
+ What covariates are prospectively identified. Is the adjusted analysis designated as the primary analysis? Are details for covariate adjustment adequately specified?
+ When exactly is the primary analysis to be done (after how many patients are accrued and at what time in followup)?
+ If there are multiple endpoints or interim analyis are there appropriate methods detailed for adjusting final P values?
+ Is there a study monitoring committee? Describe.
+ Who has access to study data and when do they have it?

Review Blank CRF

+ Evaluate those pages of blank CRF referring to critical efficacy and safety endpoints.
+ Does the CRF collect the primary data needed to support critical investigator opinions (e.g., are tumor measurements recorded to document investigator response evaluation)? If not, consider refusing to file NDA.

Conclusions from Protocol Review

+ Are primary endpoint and trial design adequate to support the labeled efficacy claim?
+ Is primary endpoint adequately defined.?
+ Are followup details adequate to provide efficacy and safety data of good quality?
+ What effect do protocol amendments have on statistical analysis and conclusions from study?
+ List issues that should be evaluated during review of study report, review of data, or by querying the applicant.

Review Study Report of Pivotal Trial

Note: As you proceed with review of the study report and of the data, refer to "factors to consider" pages for Conduct and for Results

Link to "Conduct" p. 6.4.2

Link to "Results" p. 6.4.3

Summarize Study Report

Read and summarize

+ Read and summarize applicant's findings.

+ Insert "reviewer comments" noting where study conduct or analyses described vary from those specified in protocol or in agreements (EOP2 or PreNDA).

+ Utilizing electronic document, cut and paste critical tables from study report and clearly label them as the applicant's tables.

+ Intersperse results of reviewer analyses of the data here or group them later in a separate section.

Perform minor analyses of data

+ Save in-depth analyses of data until review of the study report is complete. This prevents you from getting "lost in the data" and allows intelligent prioritization of efforts in data review.

+ However, some familiarity with case report form and data structure are helpful in understanding analyses and in generating questions during review of the study report. Selective and simple analyses of the data performed during review of study report may also decrease monotony of review.

Sponsor's conclusions

+ It may be helpful to include the sponsor's conclusions verbatim.

Meet with Statistician

Timing:

+ Best time for meeting may be after review of study report for each pivotal trial.

Participants:

+Meetings of statistical and medical teams are an integral part of planning review strategy in some divisions (e.g., DDDP). Such meetings might be considered. Currently meetings in DODP are generally informal and are limited to primary reviewers.

Goals:

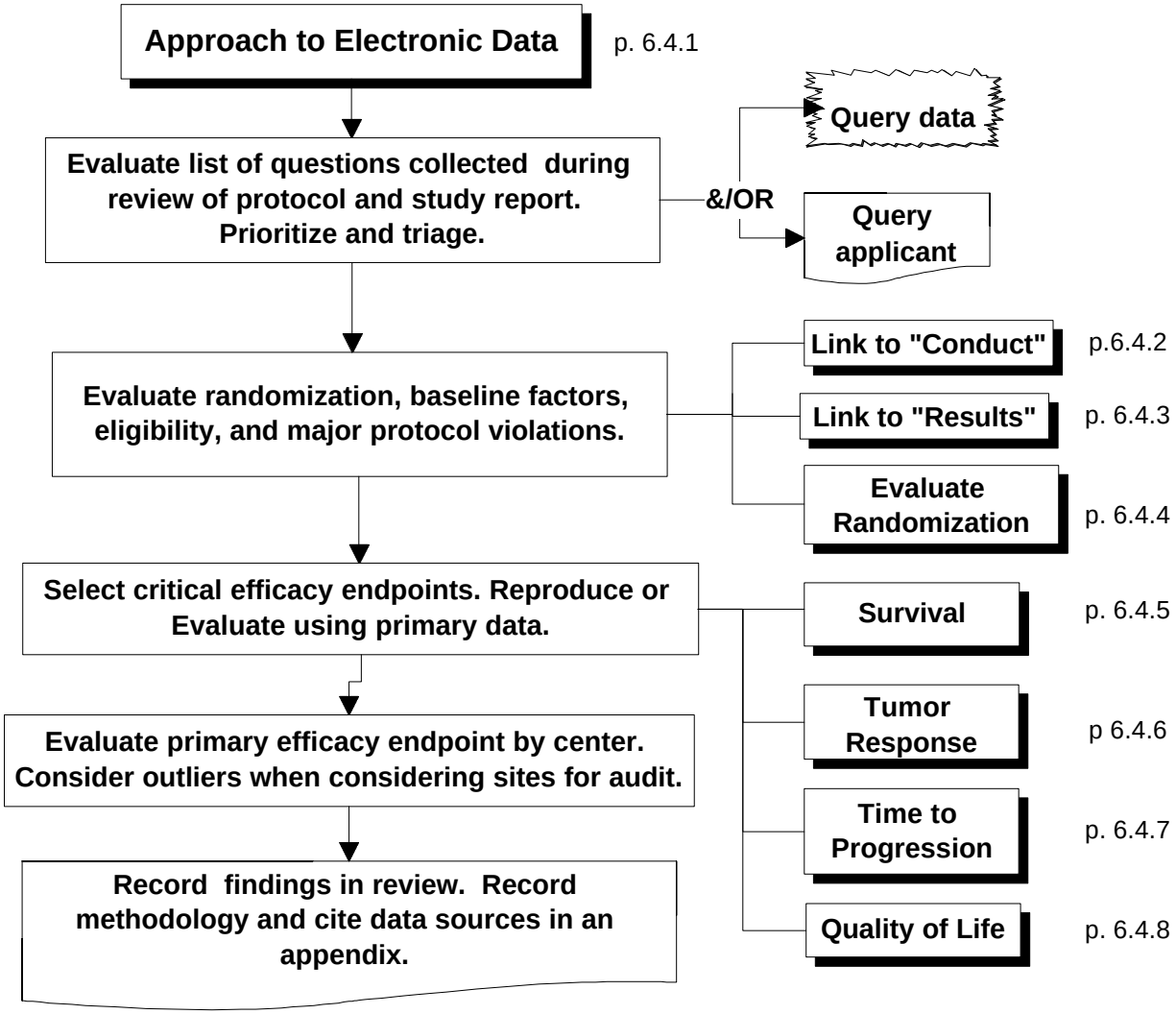
+ Agree upon primary endpoints and primary analyses.

+ Consider whether there will be joint review of the data, e.g., medical officer reassigment of outcomes to be utilized by statistician. Schedule future meetings accordingly.

+ Consider possibility of "joint-review" document.

Review of Efficacy Data

NOTE*: The individual patient data is the focal point in evaluation of the study conduct and the study results. The On Site Study audit will verify the individual patient data by comparing it to the patient's medical records, x rays and laboratory reports. The medical officer must verify that the individual patient data reported in the NDA was used by the applicant in the tables and data analyses reported in the NDA. This can only be done by the reviewer performing the analyses him or herself and replicating the applicant's results. The statistician may assist in this task. This confirms the applicant's calculations and also that the applicant used the individual patient data reported in the NDA to do the analyses. It is not necessary to replicate all of the applicant's analyses, but the most important ones should be done.



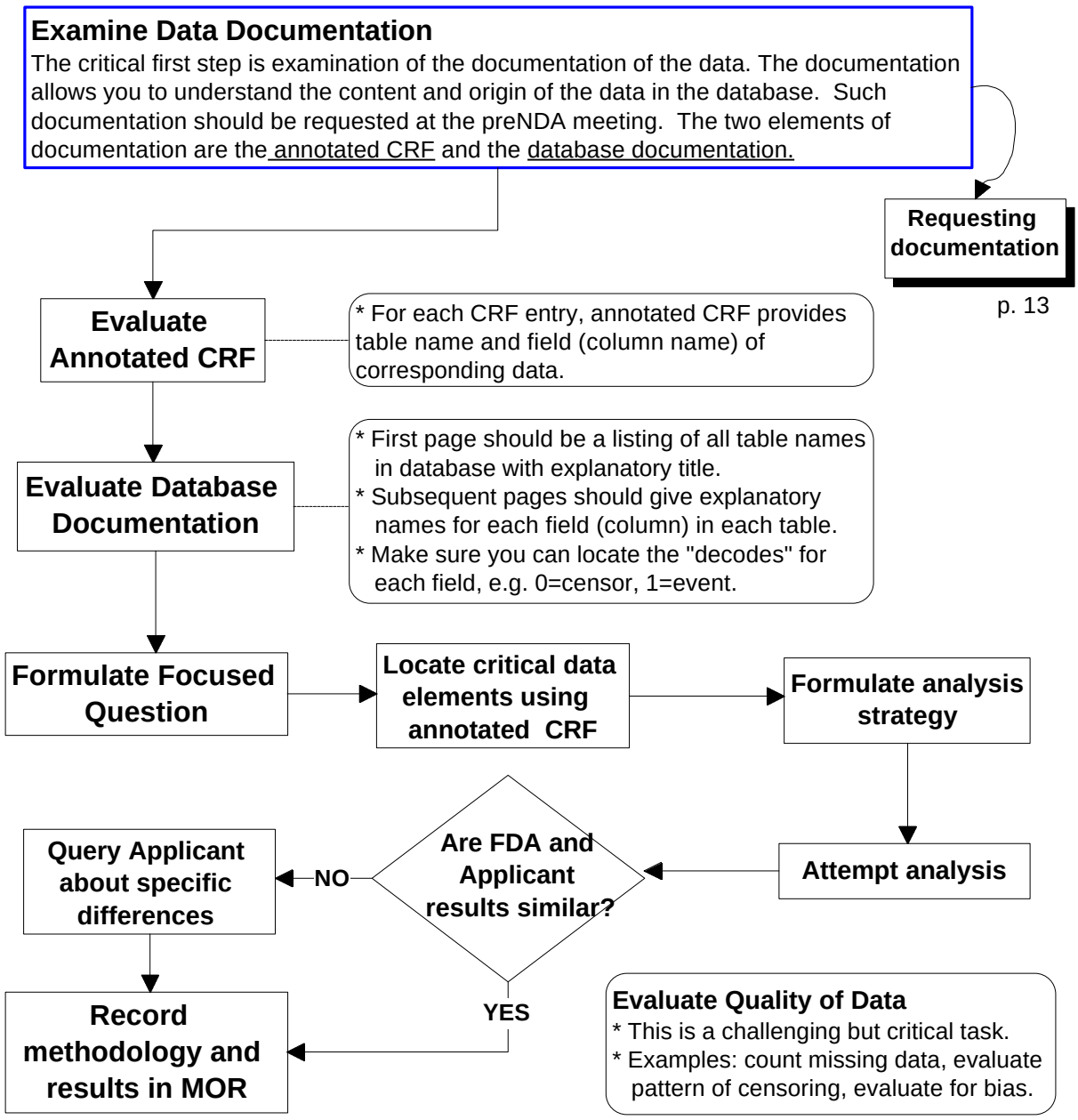
* Derived from document by John R Johnson, MD

Approach to Electronic Data

Introductory Comments

1. Evaluation of data should be focused and should be performed after you have reviewed the protocol and study report.

2. Some data fields are not primary data from the audited case report form but are derived or "transformed" data. For example, tumor progression date is derived from tumor measurement data. In general, perform analyses starting with primary data identical to that entered on the CRF.



Factors to consider in evaluating Conduct of Pivotal Trials*

1. Eligibility. Were the eligibility criteria met? For each patient declared ineligible by the applicant the patient's data should be reviewed to confirm the ineligibility. The ineligible/inevaluable patients should be less 5% of the total. Greater than 10% indicates poor study conduct which probably extends to all aspects of the study.

2. Randomization. Was the randomization procedure described in the protocol followed?

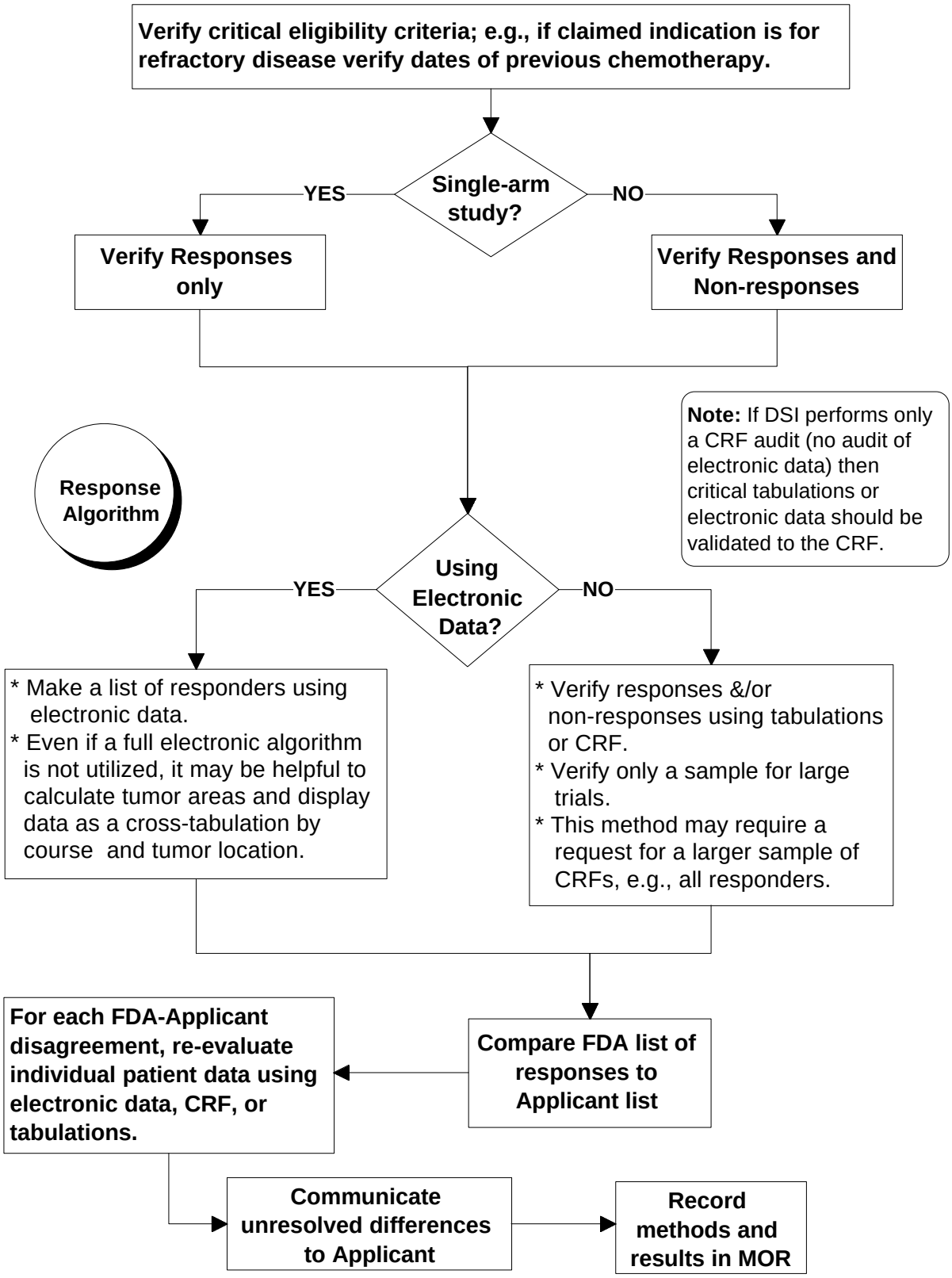
3. Treatment. Did the patient receive the correct drug(s) at the correct dose and schedule and for the correct duration? Were the protocol prescribed dose adjustments, drug holding and drug discontinuation procedures followed?

4.Efficacy. Was each efficacy endpoint measured at the time(s) and in the manner described in the protocol?

5.Safety. Was each safety endpoint measured at the time(s) and in the manner described in the protocol?

*From outline by John R. Johnson, MD

Review of Tumor Response



Evaluate randomization

Comment: Verifying randomization is difficult if not impossible for a reviewer. The following methods may give clues that suggest problems in the randomization process. Such suspicions should be communicated to DSI so that appropriate attention may be focused on randomization during the audit.

Understand the Randomization Process

* Was there a screening list?

* Ask Applicant how patient ID numbers were generated. Were numbers generated consecutively as randomized?

* Was the randomization process stratified?

* Was it blocked? If so what were the block sizes?

Sort by date; are ID numbers consecutive?

Examine balance within randomization blocks

* Check the data tabulations to see if randomization lists are displayed according to stratification cell. Individuals listed by randomization date should balance within randomization blocks (see below for example).

This analysis may be performed electronically:

Group data by each stratification factor, sort by randomization date, and display treatment arm. The following is an example:

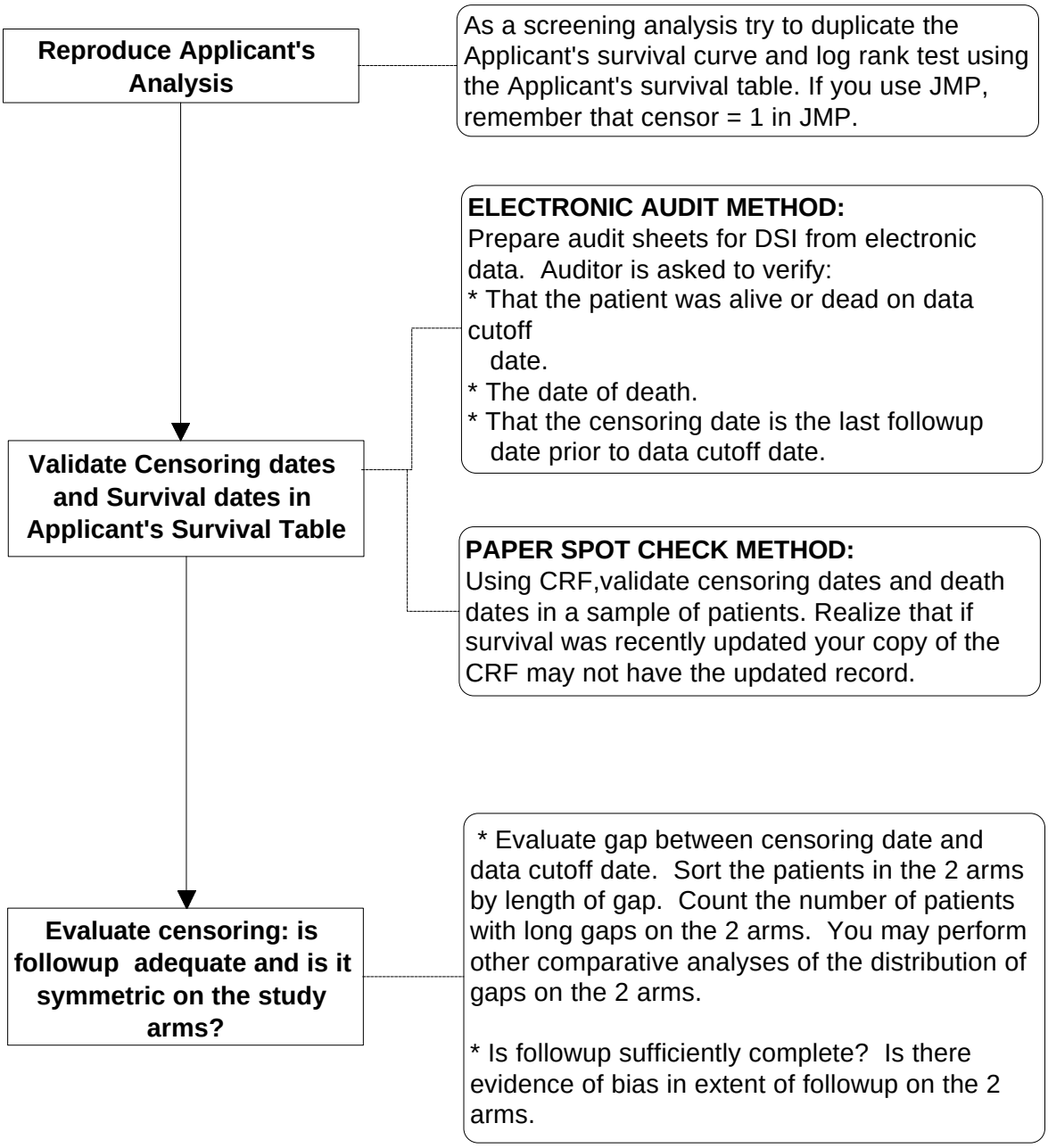
Randomization is in permuted blocks of 4. Treatment is stratified by performance status(0-1 vs 2-4) and by center. A query is performed sorting by center, PS, and then by randomization date. This gives the following results:

Center	PS	Treatment Arm
1	0-1	A
1	0-1	B
1	0-1	B
1	0-1	A
1	2-4	B
1	2-4	B
1	2-4	A
1	2-4	B

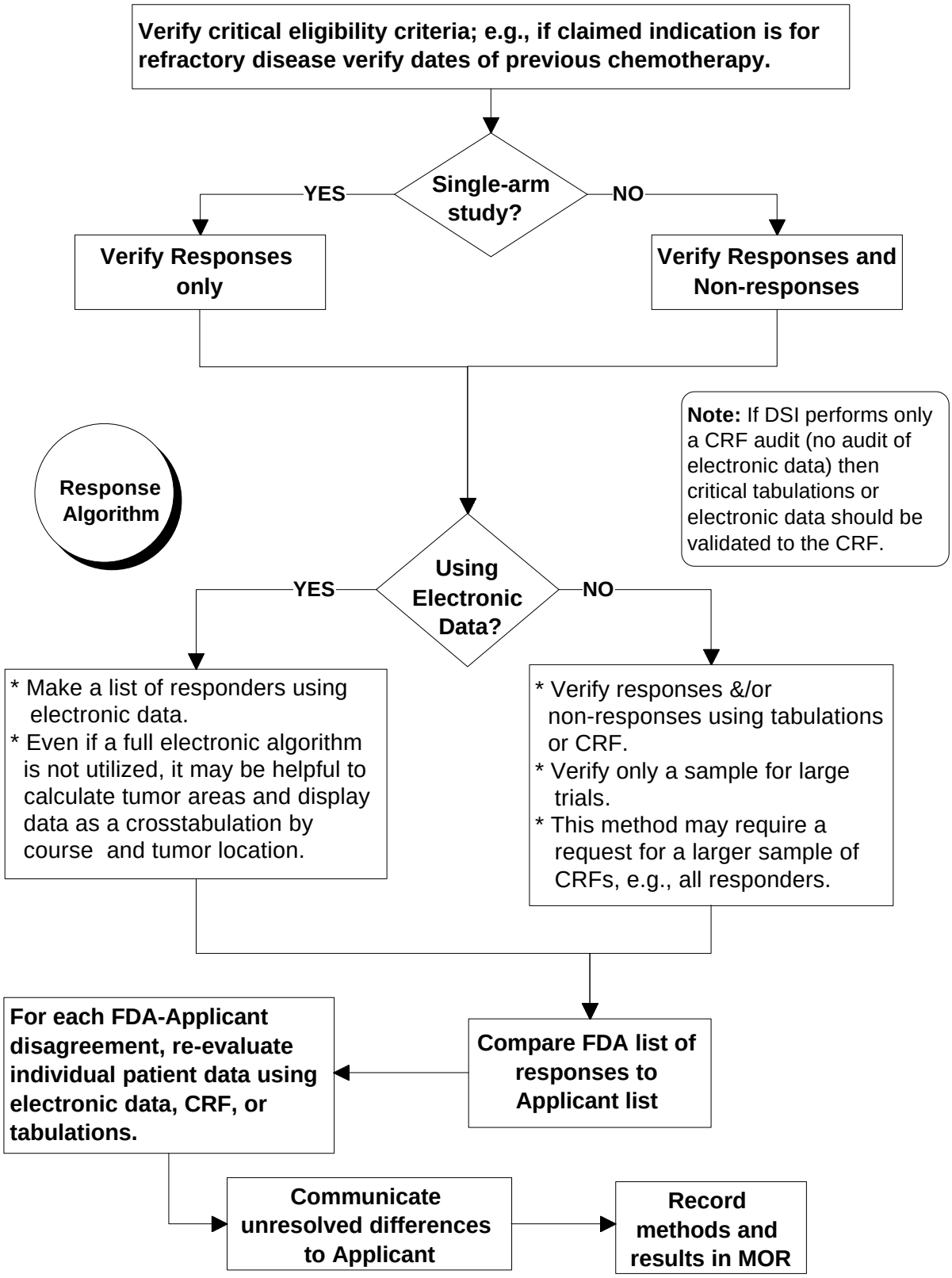
In the first cell (Center = 1, PS = 0-1) the first block of 4 is balanced with 2 A's and 2 B's. However in the second cell (Center = 1, PS = 2-4), there are more B's than A's . There is an error in randomization. One cause of such an error is dropping a patient from the rolls after randomization.

Look for imbalances in baseline factors using multivariate analysis

Review of Survival

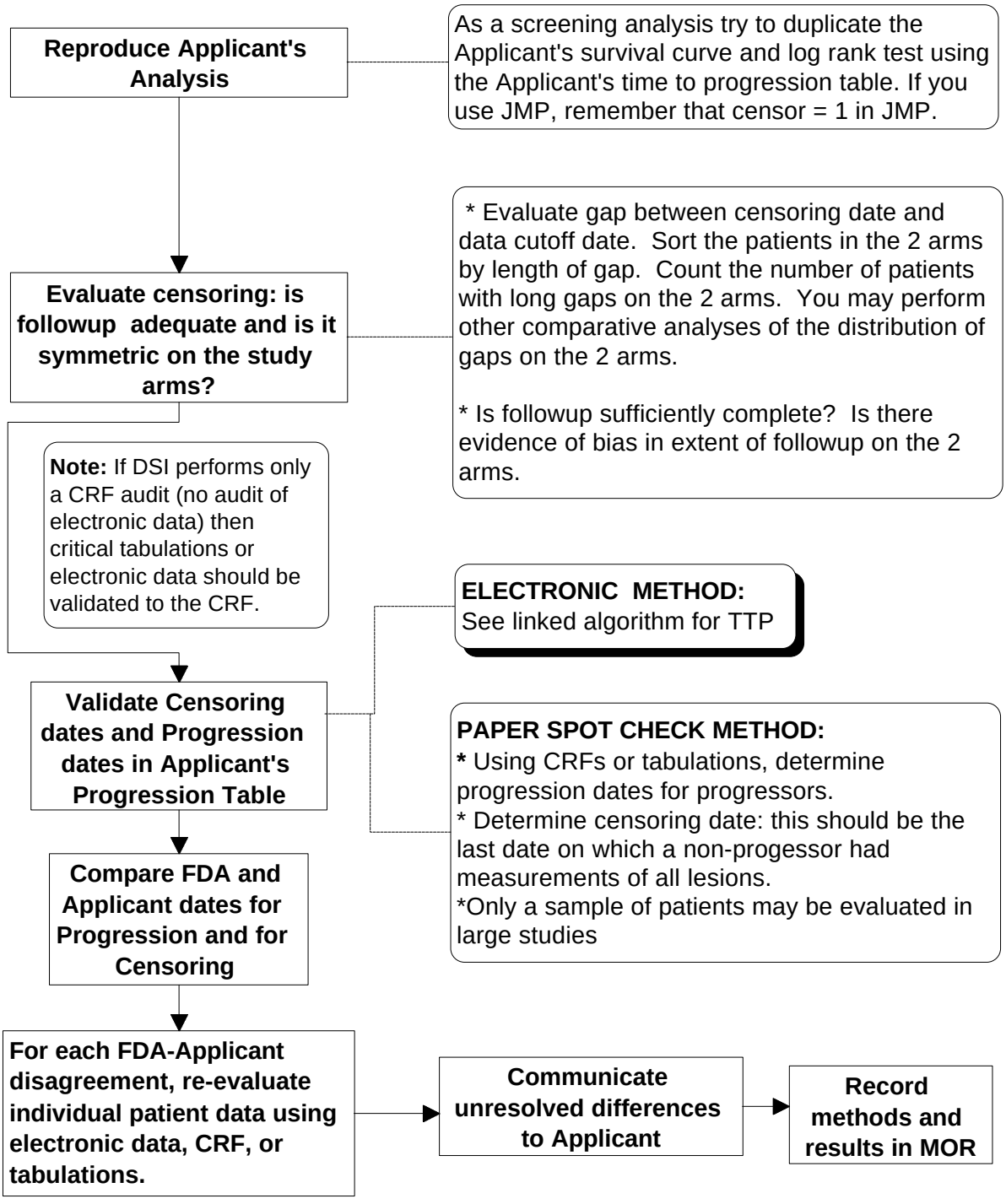


Review of Tumor Response



Review of Time to Progression

Comment: Time to progression is a fickle endpoint that is difficult to validate from the primary tumor data. The endpoint synthesizes data from numerous tumor measurements, often combined with subjective investigator assessments. If this is a critical endpoint for NDA approval, it is important for the reviewer to attempt to valildate the sponsor analysis, starting from raw tumor measurements.



Review of Quality of Life

Review of QOL data is complicated and should be done with a statistician who is expert in this area. Consider the following points:

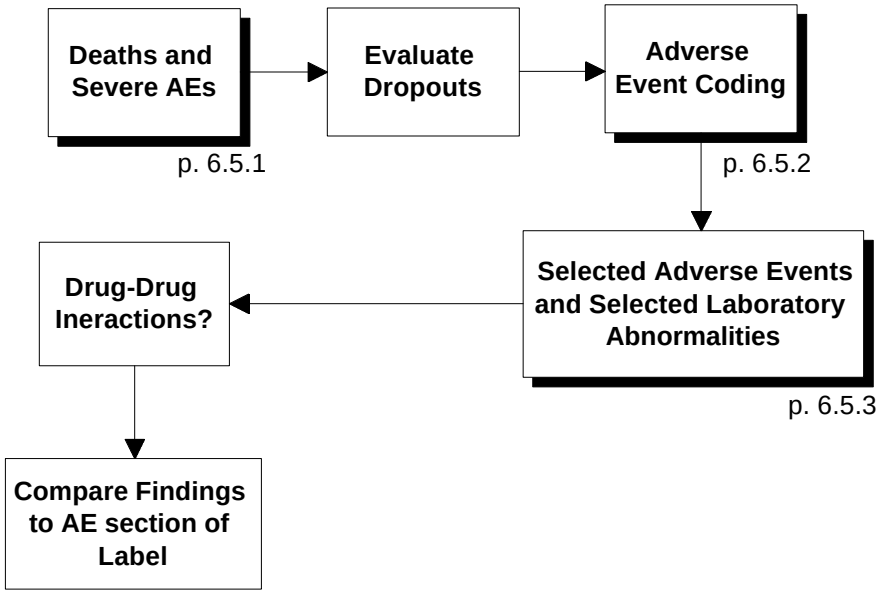
* Is the QOL instrument validated?
* Do the measurements represent clinical benefit? Is the size of the treatment effect clinically significant?
* Is the study blinded? If not blinded, can one exclude bias as the reason for the apparent treatment effect.
* Was the analysis plan pre-specified?
* Have p values been corrected for multiple comparisons?
* Has DDMAC been consulted whether QOL claims should be included in the label? Does labeling also include negative QOL results?
* Evaluate missing data. Does the amount of missing data preclude analysis? Are appopriate methods used for handling missing data (consult with statistician)?

Safety Review

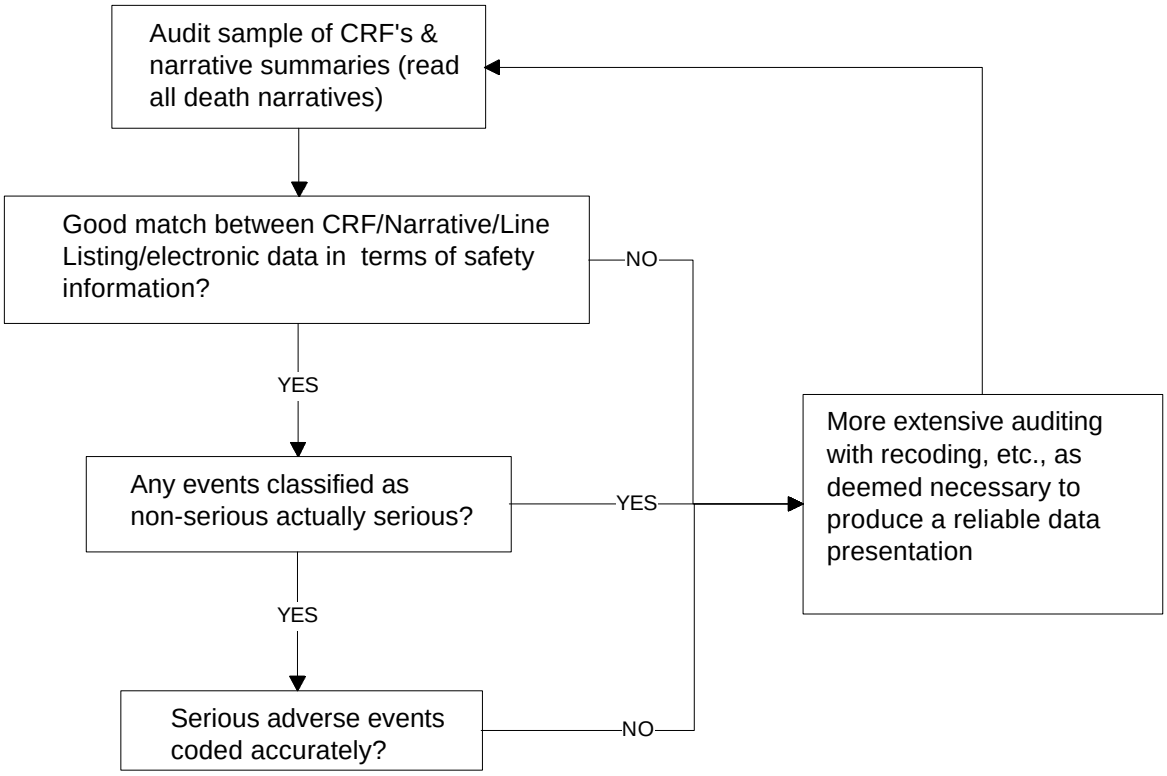
The safety review of anticancer drugs differs from the safety review of many drugs. Drugs in both study arms of randomized cancer clinical trials are often known to be toxic. The disease, cancer, has severe manifestations that may be difficult to distinguish from drug toxicity; safety conclusions are usually based on differences in comparison to a toxic control drug in a randomized controlled trial. Safety data cannot usually be pooled across trials, so the integrated summary of safety is usually not more revealing than summaries of each of the controlled trials. To the right of this text box are links to 2 documents describing the safety review as performed in other CDER divisions. At times, especially when evaluating less toxic agents such as hormones, it may be helpful to consider the methodologies described in these documents.

Safety Review Outline (Dubitsky, DNDP)

CDER Draft Safety Reviewer Guidance

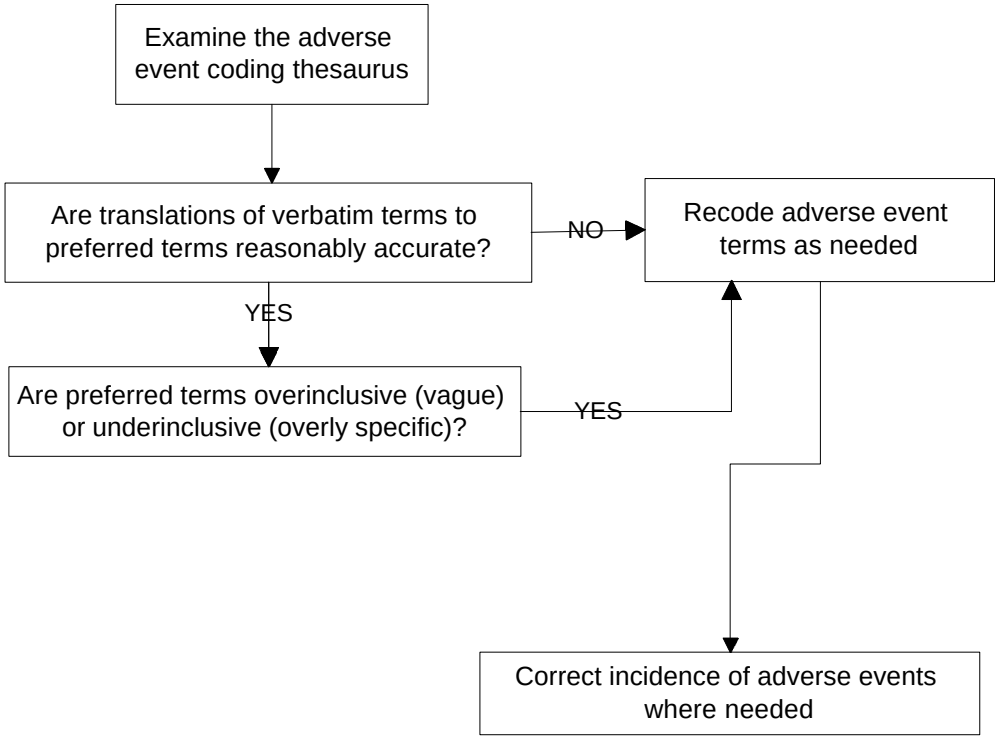


REVIEW OF DEATHS WITHIN 30 DAYS OF TREATMENT AND SERIOUS ADVERSE EVENTS*



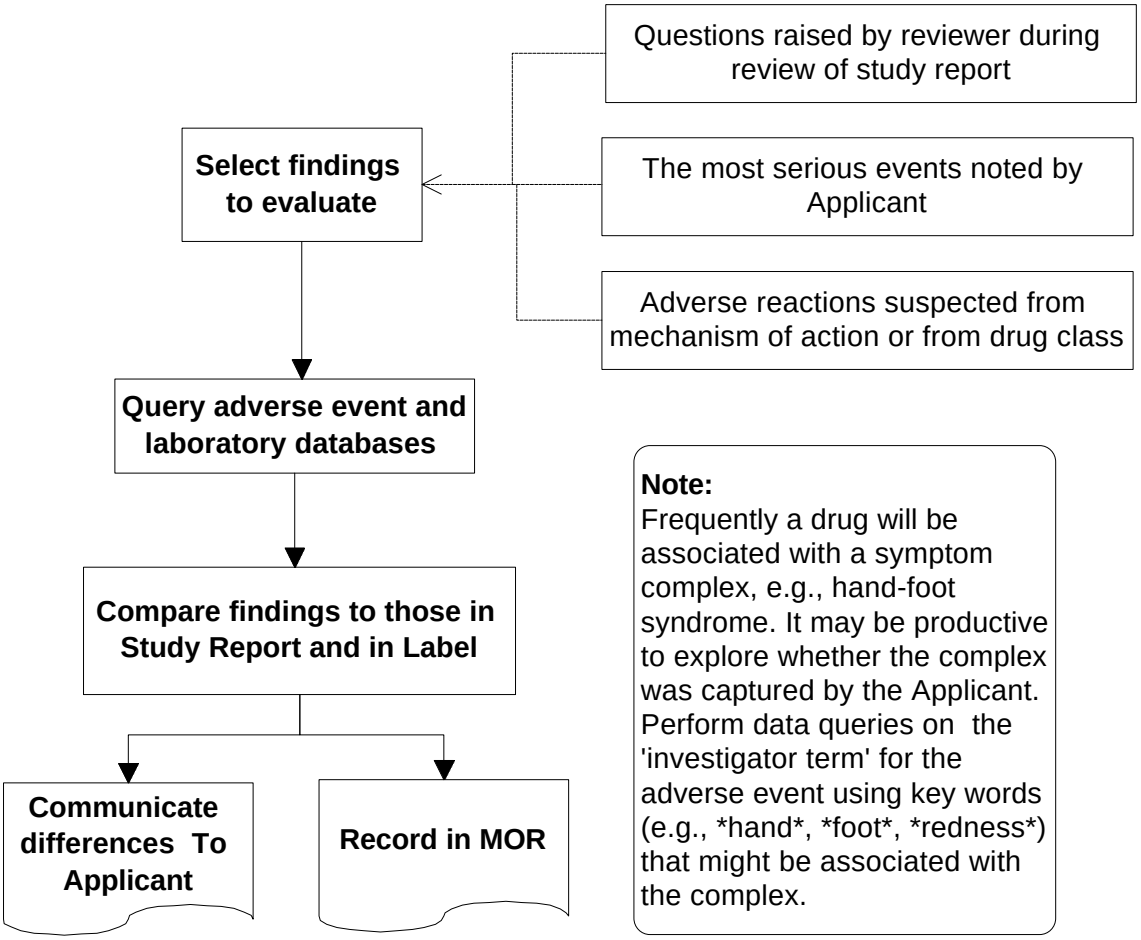
*Page derived from DNPDP, Dubitsky.

EVALUATE CODING OF ADVERSE EVENTS*

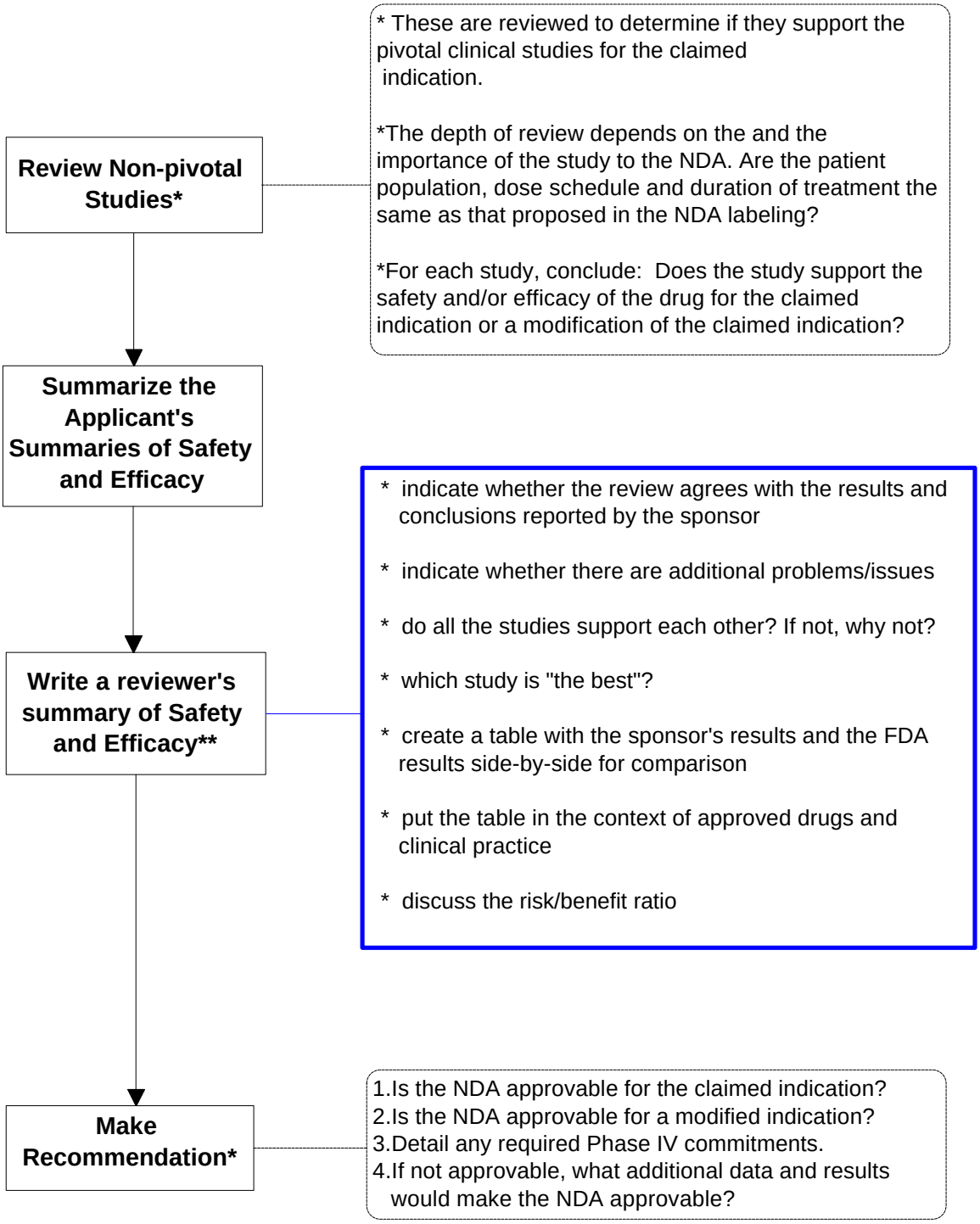


* Page derived from Dubitsky/DNPDP.

Selected Adverse Events and Selected Laboratory Abnormalities



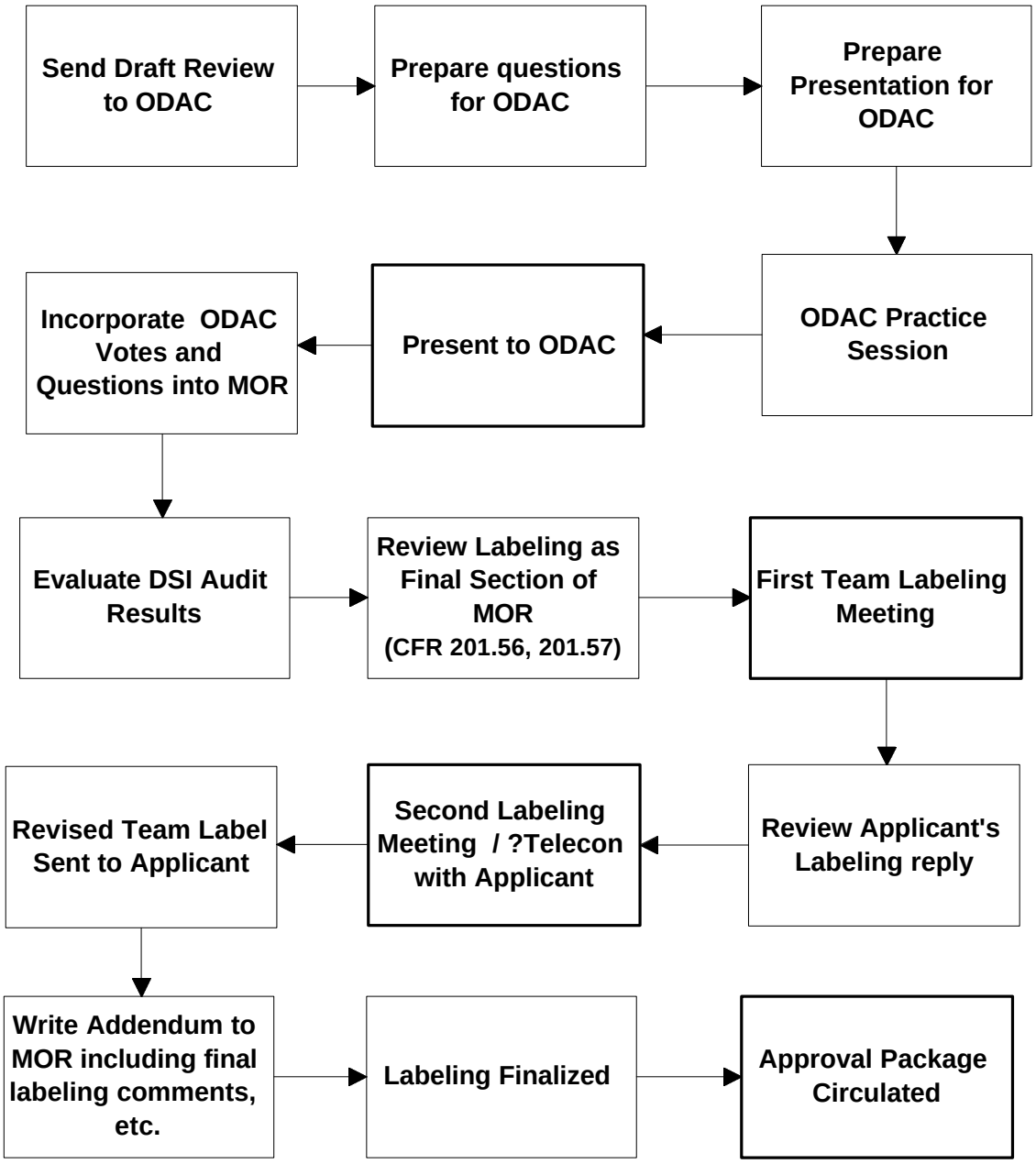
Finish Draft Review



* From review outline by John Johnson

** From review diagram by Susan Honig

Activities after ODAC and before Approval



1 Title and General Information
- 1.1 Title/Heading - Medical Officer's Review
  - 1.1.1 NDA #
  - 1.1.2 M.O. Review #
  - 1.1.3 Submission (date)
  - 1.1.4 Review completed (date)
- 1.2 Drug name
  - 1.2.1 Generic name
  - 1.2.2 Proposed trade name
  - 1.2.3 Chemical name (structure optional)
- 1.3 Sponsor
- 1.4 Pharmacologic Category
- 1.5 Proposed Indication(s)
- 1.6 Dosage Form(s) and Route(s) of Administration
- 1.7 NDA Drug Classification
- 1.8 Important Related Drugs
- 1.9 Related Reviews (statistics, biopharm, consults, etc.)

2 Table of Contents (use decimal system to number pages)

3 Material Reviewed (volume numbers which serve basis for this review)

4 Chemistry/Manufacturing Controls

5 Animal Pharmacology/Toxicology

6 Clinical Background
- 6.1 Relevant human experience
- 6.2 Important information from related INDs and NDAs
- 6.3 Foreign experience
- 6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics
- 6.5 Other relevant background information (meetings, commitments)
- 6.6 Directions for Use

7 Description of Clinical Data Sources (both IND and non-IND)
- 7.1 Study Type and Design/Patient Enumeration, Demographics, Extent of Exposure
- 7.2 Post-Marketing Experience
- 7.3 Literature

8 Clinical Studies
- 8.1 Indication # 1
  - 8.1.1 Trial # 1
    - 8.1.1.1 Objective/Rationale
    - 8.1.1.2 Design
    - 8.1.1.3 Protocol
      - 8.1.1.3.1 Population, procedures
      - 8.1.1.3.2 Endpoints
      - 8.1.1.3.3 Statistical considerations
    - 8.1.1.4 Results
      - 8.1.1.4.1 Patient Disposition, comparability
      - 8.1.1.4.2 Efficacy endpoint outcomes
      - 8.1.1.4.3 Safety comparisons
    - 8.1.1.5 Reviewer's Comments/Conclusions of study Results
  - 8.1.2 Trial # 2
- 8.2 Indication # 2

9 Overview of Efficacy - Comparative results between studies

10 Overview of Safety (including data quality)
- 10.1 Significant/Potentially Significant Events
  - 10.1.1 Deaths
  - 10.1.2 Other Significant/Potentially Significant Events
  - 10.1.3 Overdosage exposure
- 10.2 Other Safety Findings
  - 10.2.1 ADR Incidence Tables
  - 10.2.2 Laboratory Findings, Vital Signs, ECGs
  - 10.2.3 Special Studies
  - 10.2.4 Drug-Demographic Interactions
  - 10.2.5 Drug-Disease Interactions
  - 10.2.6 Drug-Drug Interactions
  - 10.2.7 Withdrawal Phenomena/Abuse Potential
  - 10.2.8 Human Reproduction Data

11 Labeling Review
- 11.1 Description
- 11.2 Clinical Pharmacology
- 11.3 Indications and Usage
- 11.4 Contraindications
- 11.5 Warnings
- 11.6 Precautions
  - 11.6.1 General
  - 11.6.2 Information for patients
  - 11.6.3 Laboratory tests
  - 11.6.4 Drug interactions
  - 11.6.5 Carcinogenesis, mutagenesis, impairment of fertility
  - 11.6.6 Pregnancy
  - 11.6.7 Labor and delivery
  - 11.6.8 Nursing mothers
  - 11.6.9 Pediatric use
- 11.7 Adverse Reactions
- 11.8 Drug Abuse and Dependence
- 11.9 Overdosage
- 11.10 Dosage and Administration
- 11.11 How Supplied

12 Conclusions

13 Recommendations
- 13.1 Approval, Approvable, Non-approval
- 13.2 Phase 4 Studies
- 13.3 Labeling
- 13.4 Other

PREPARATION FOR SUBMISSION OF DATA TO DODP: p. 13.0
PreNDA ADVICE TO SPONSOR

The following critical elements of an electronic submission should be submitted concurrent with your NDA:

- All primary data in a usable format
- Adequate documentation of the data
- Electronic copies of study reports, protocols, integrated summaries, and labeling, preferably in a current version of Word.
- A detailed analysis plan for each critical endpoint.

1. Primary data

All information from the case report form recorded in electronic form should be submitted in a format useful to the medical and statistical reviewers. SAS transport files (*.xpt) will generally suffice. Reviewers may occasionally request other formats.

2. Data documentation

Adequate documentation of the data is critical. Two essential forms of documentation are the Annotated Case Report Form and the Detailed Data Definition. The annotated case report form is an example CRF mapping each blank on the case report form to the corresponding element in the data base. Each page and each blank of the CRF should be represented. You should write "not entered in data base" in all sections where this applies. The data definition is an organized listing of all tables with corresponding fields, field names, data types, codes (and decodes), and narrative descriptions. It should indicate which fields contain primary data (from CRF) and which contain derived data. One useful method for presenting the detailed data definition is to include all such defining elements in one large electronic table; this allows one to electronically search the data definition elements.

Statisticians using SAS will generally request SAS DATA SETS and the SAS CODE used for analyzing the data. In addition to the documentation noted above, statisticians often request SAS PROC CONTENTS output for each data set, a printout of a few observations from each file, and formats and coding descriptions of variables.

3. Detailed analysis plan

During NDA review, the reviewer will use primary data from the case report form (or its electronic counterpart) to verify critical analyses. Please detail how the specific database elements (or annotated case report form elements if electronic data cannot be utilized) can be transformed and analyzed to produce your study results.

The reviewer has identified the following critical endpoints for this study:

a.
b.
c.
d.

For each of these critical endpoints:

- List all data elements from the annotated case report form that are utilized in the analysis.
- Present a detailed plan for how these data are utilized. Include contingencies for missing data, duplicate data, etc. The attached algorithm for response rate demonstrates the level of detail that may be needed for complex endpoints. For time-to-event endpoints detail the selection of censoring dates.

4. Example electronic table for data on tumor response

If possible, submit data on tumor response in an electronic table with the following fields (see attached example table)

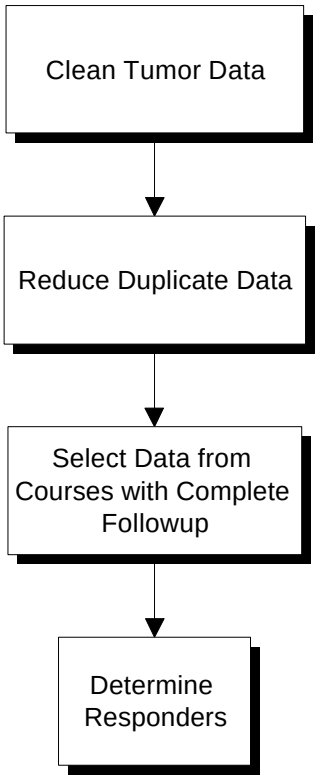
ID: Unique patient ID
Visit: Visit number for grouping measurements. State how data were parsed into visits.
Date: Date of observation.
LesionID: Consecutive series of numbers or letters uniquely representing each lesion in a patient.
Lsite: Name of lesion site, text.
MeasEval: Measurable or evaluable lesion?
Method: Method of measurement. Reduce to common terms (CT, CXR, MRI, US, PE, etc.)
M1text: Tumor measurement, largest dimension. May include text entries if needed.
M2text: Tumor measurement, perpendicular to M1. May include text entries if needed.
M1num: Tumor measurement, largest dimension, numerical format.
M2num: Tumor measurements, perpendicular to M1, numerical format.
EvalDzResp: Status of evaluable lesion (PRESENT, CR, PROG)
DataComment: Comments about data including how text comments (such as "no change") were converted into numerical values.
NewLesion: New lesion? (Y, N)
PatientResp: Applicant overall response assessment of all lesions at this visit (CR, PR, SD, PROG).
ConfirmedResp: Response status confirmed after 28 days (CR, PR, NA).

5. Sites for Audit by DSI

For the critical studies there please submit a list of the investigative sites, principal investigators (with full addresses), numbers of patients at each site, and efficacy outcomes for the primary endpoint at each site.

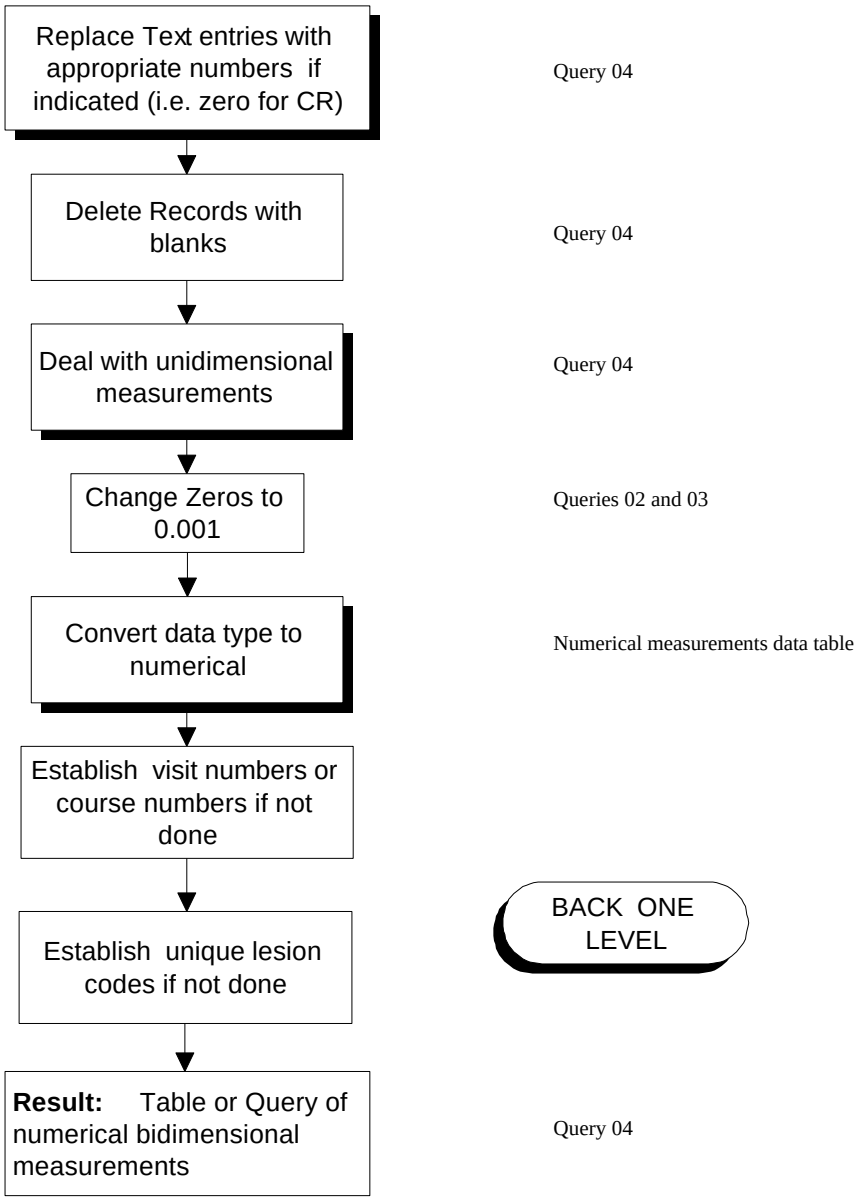
C:\$CREATIV\Response\RespPdf\RespPdf.abc

AN ALGORITHM FOR DETERMINING TUMOR RESPONSE



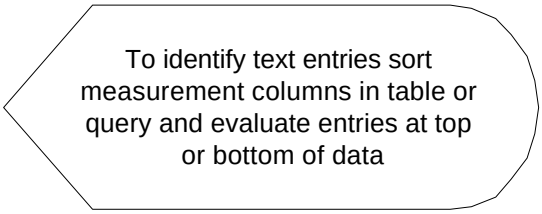
C:\$CREATIV\Response\Link2.abc

CLEAN TUMOR DATA



C:\$CREATIV\Response\Link6abc

Replace Text Entries with Numbers



C:\$CREATIV\Response\Link7abc

Deal with unidimensional measurements

-Identify unidimensional measurements using queries containing "null" or other appropriate value in one measurement field and "not null" in the second field.*

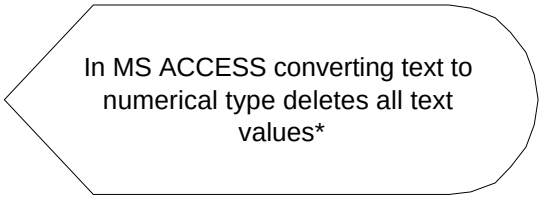
-Consider deleting record, replacing blank with the value of measurement #,1 replacing blank with zero, or perhaps analyzing data several ways.

*Query 01

BACK ONE LEVEL

C:\$CREATIV\Response\Link8.abc

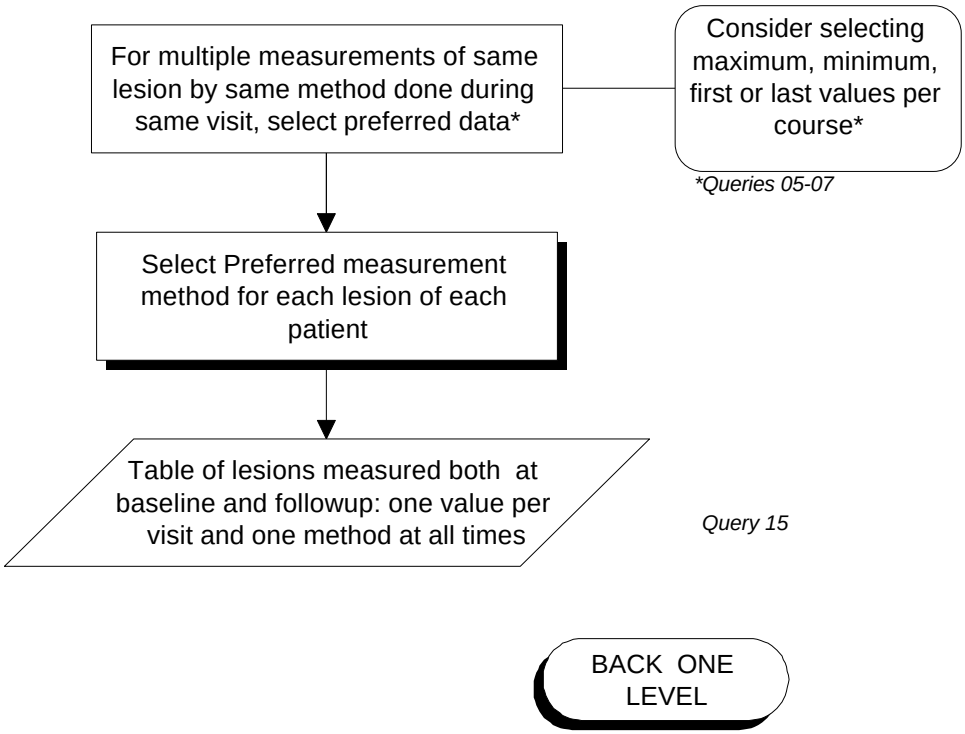
Convert Data Type to Numerical



*See 'numerical measurements data table'

C:\$CREATIV\Response\Link3.abc

Reduce Duplicate Data
(same lesion, same course)



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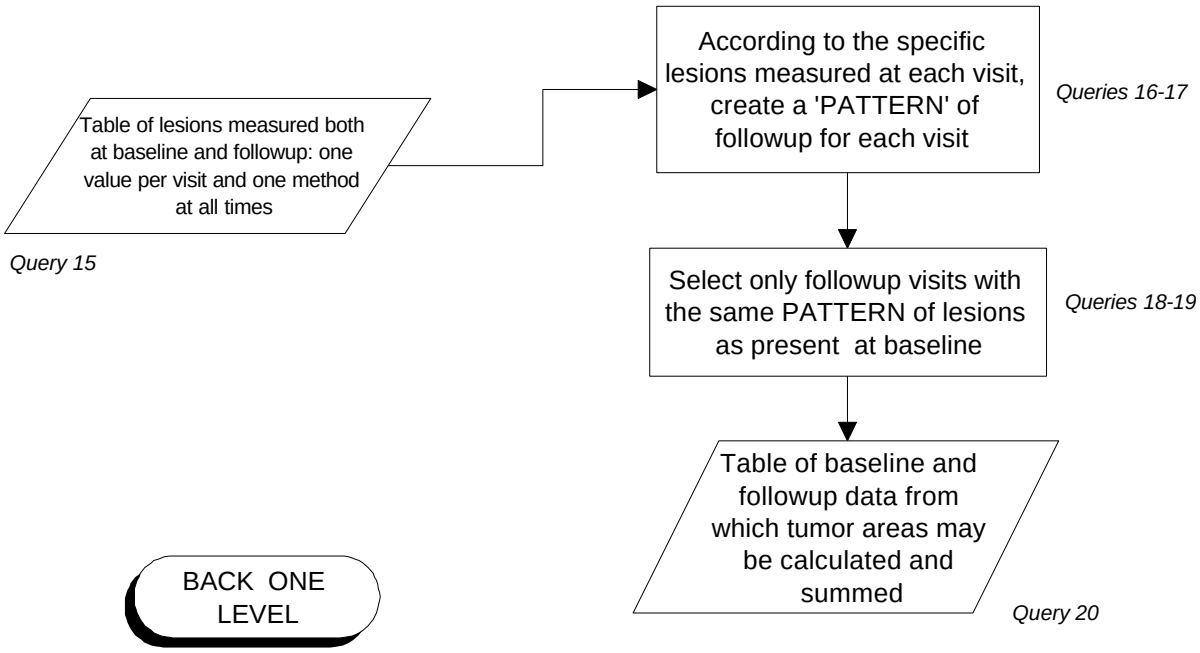
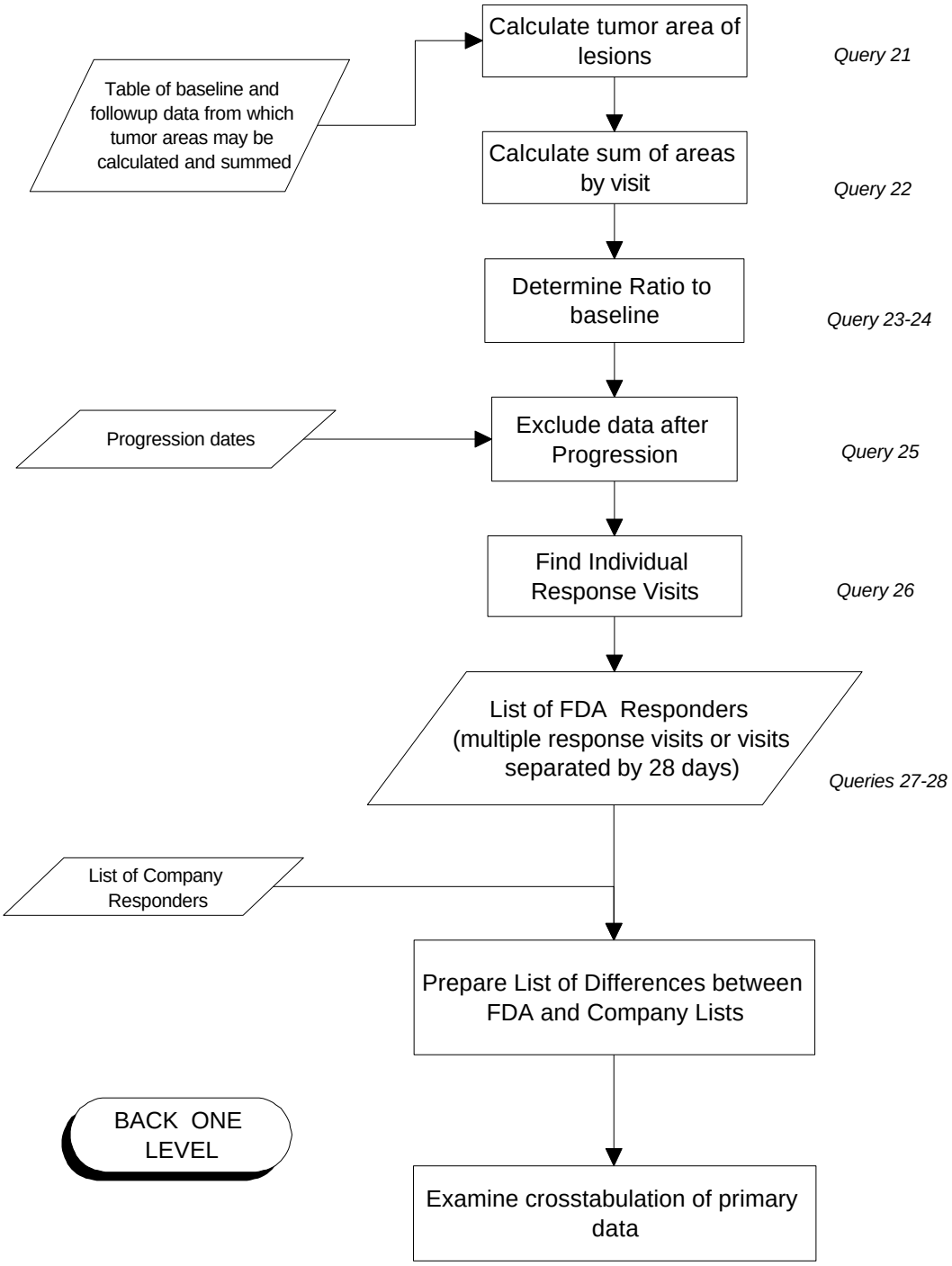
Select Followup Courses with Same Lesions as Baseline



C:\$CREATIV\Response\Link46abc

Determine Responders



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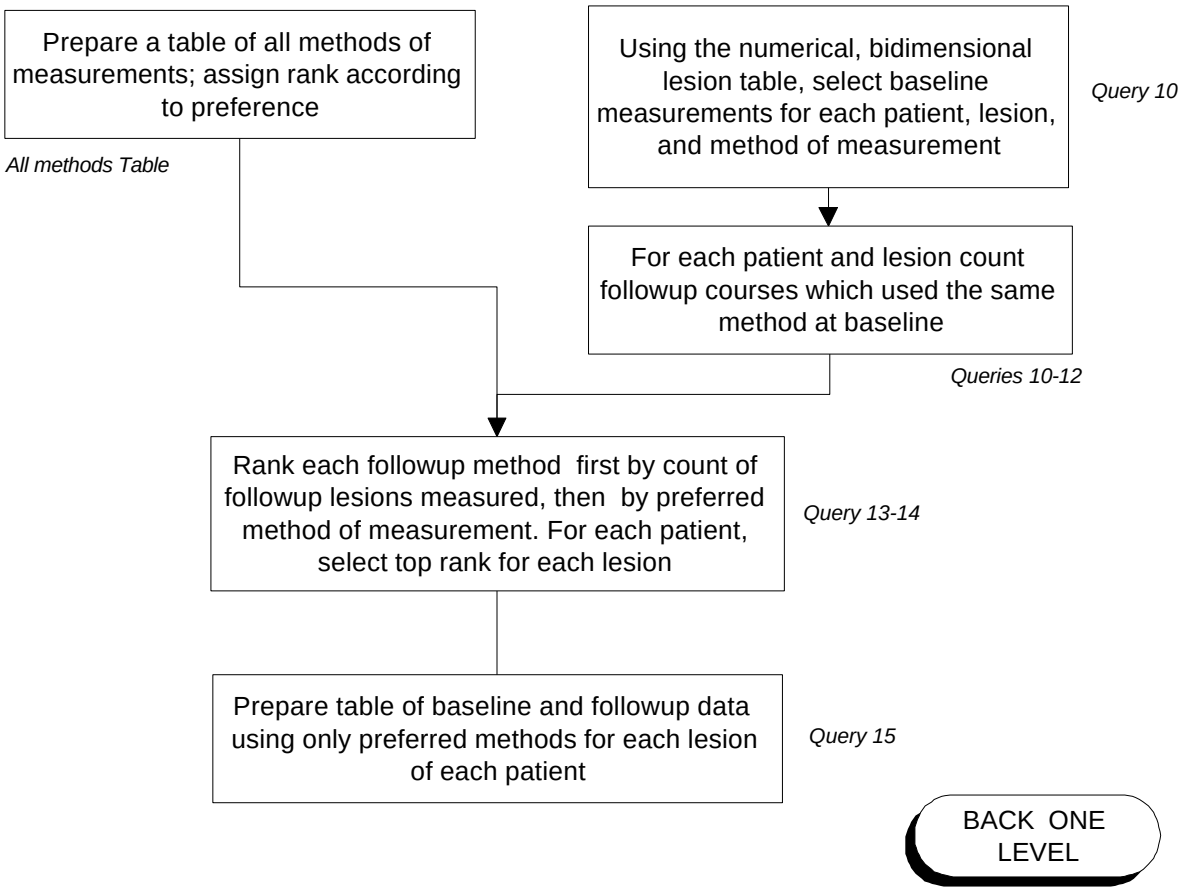
Select Preferred Measurement Method for Each Lesion of Each patient



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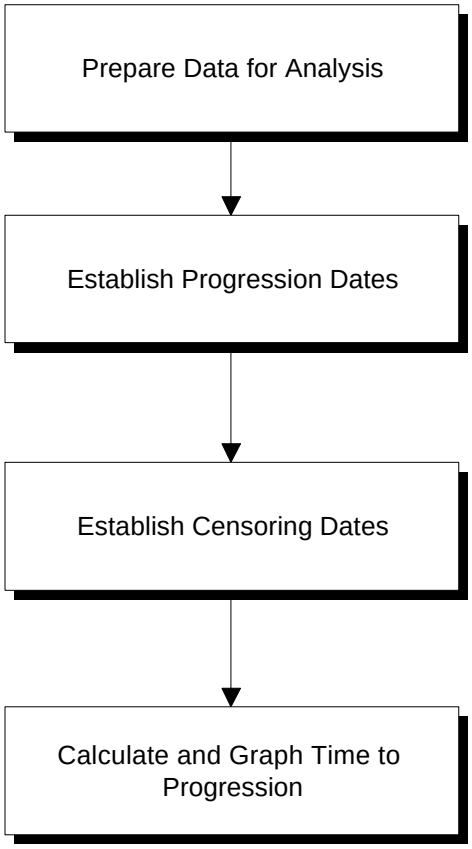
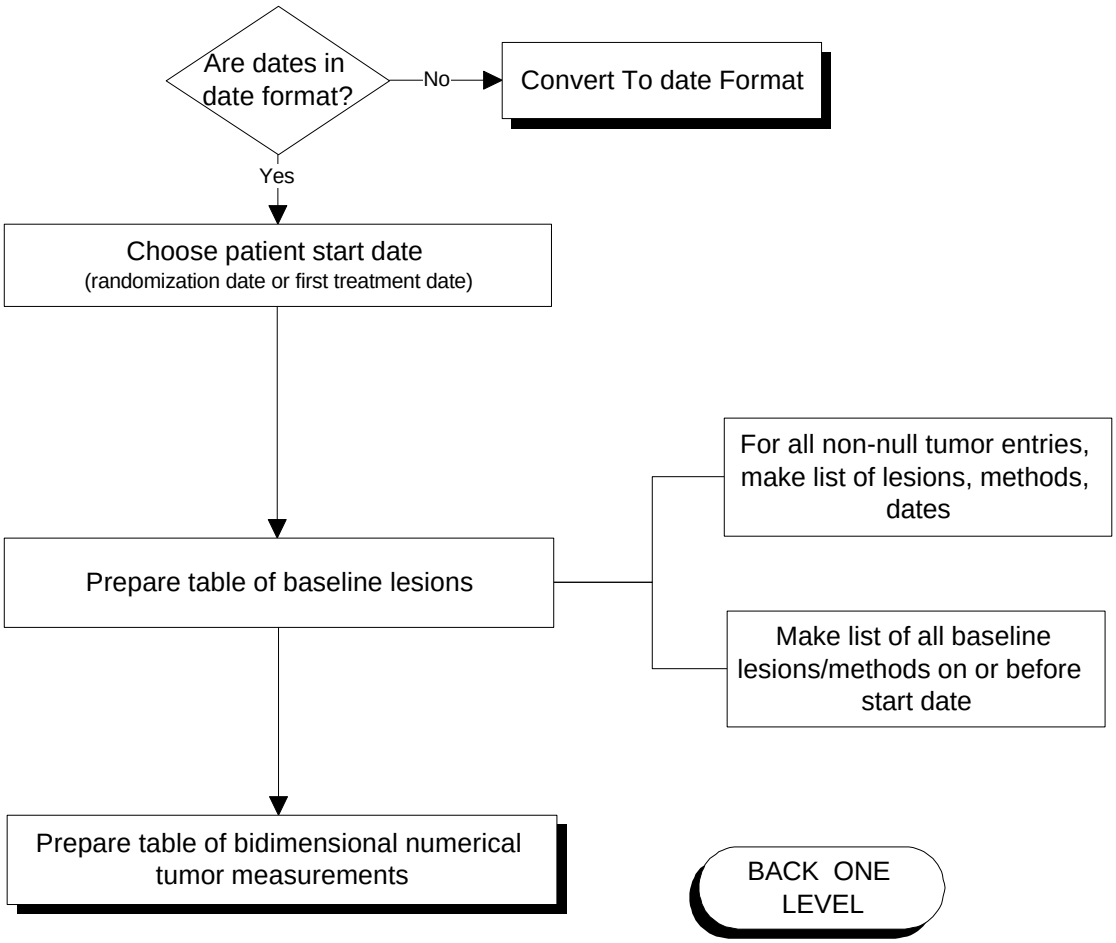
AN ALGORITHM FOR TIME TO PROGRESSION



C:\$CREATIV\Progress\Link2.abc



C:\$CREATIV\Progress\Link4.abc

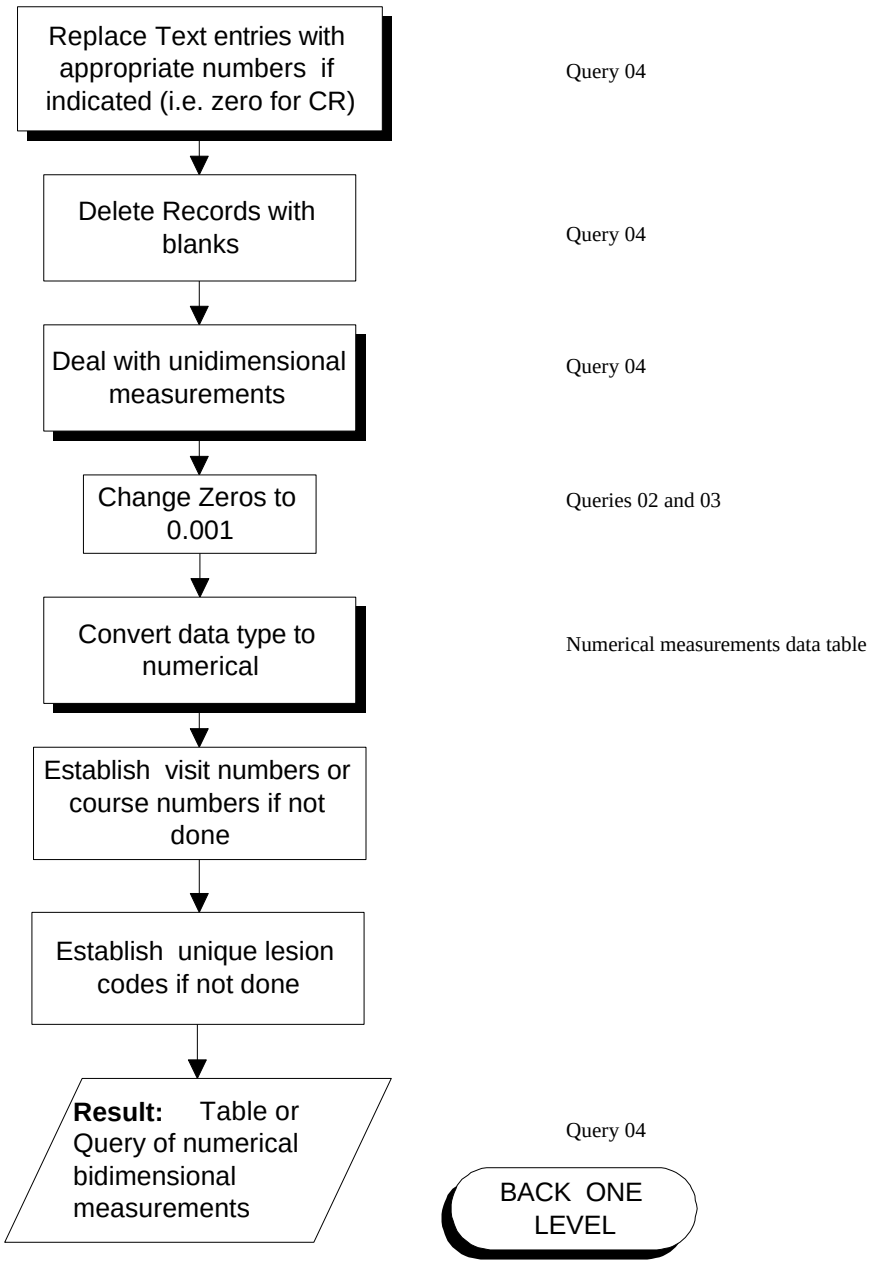
1. Even if dates are in text format, if written certain style, format may be converted using design view of Access tables.

2. If date style is not accepted by Access try the following method.:
   -Copy the date column into the windows clipboard.
   -Paste into MS Excel.
   -Convert to serial number using Date Value function in Excel
   -Create a new field (number format) in Access table, and paste these values into it.
   -Convert the data type of this column to date in table design.

BACK ONE LEVEL

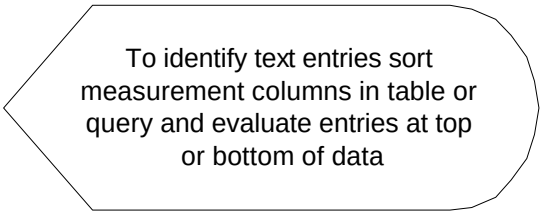
C:\$CREATIV\Progress\Link3.abc

CLEAN TUMOR DATA



C:\$CREATIV\Response\Link6abc

Replace Text Entries with Numbers



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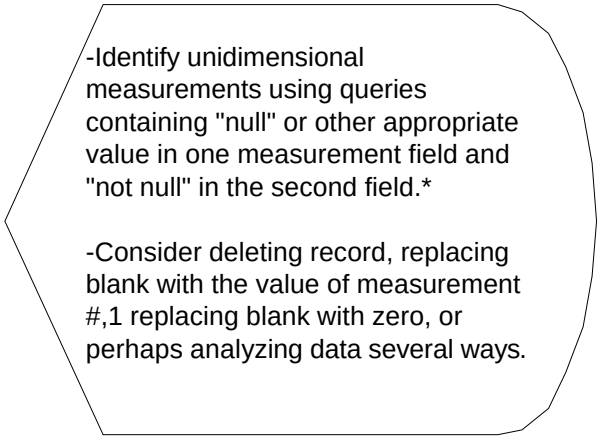
Deal with unidimensional measurements

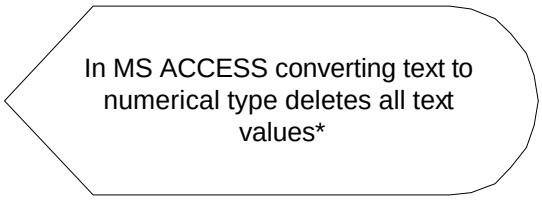


*Query 01

BACK ONE LEVEL

C:\$CREATIV\Response\Link8.abc

Convert Data Type to Numerical

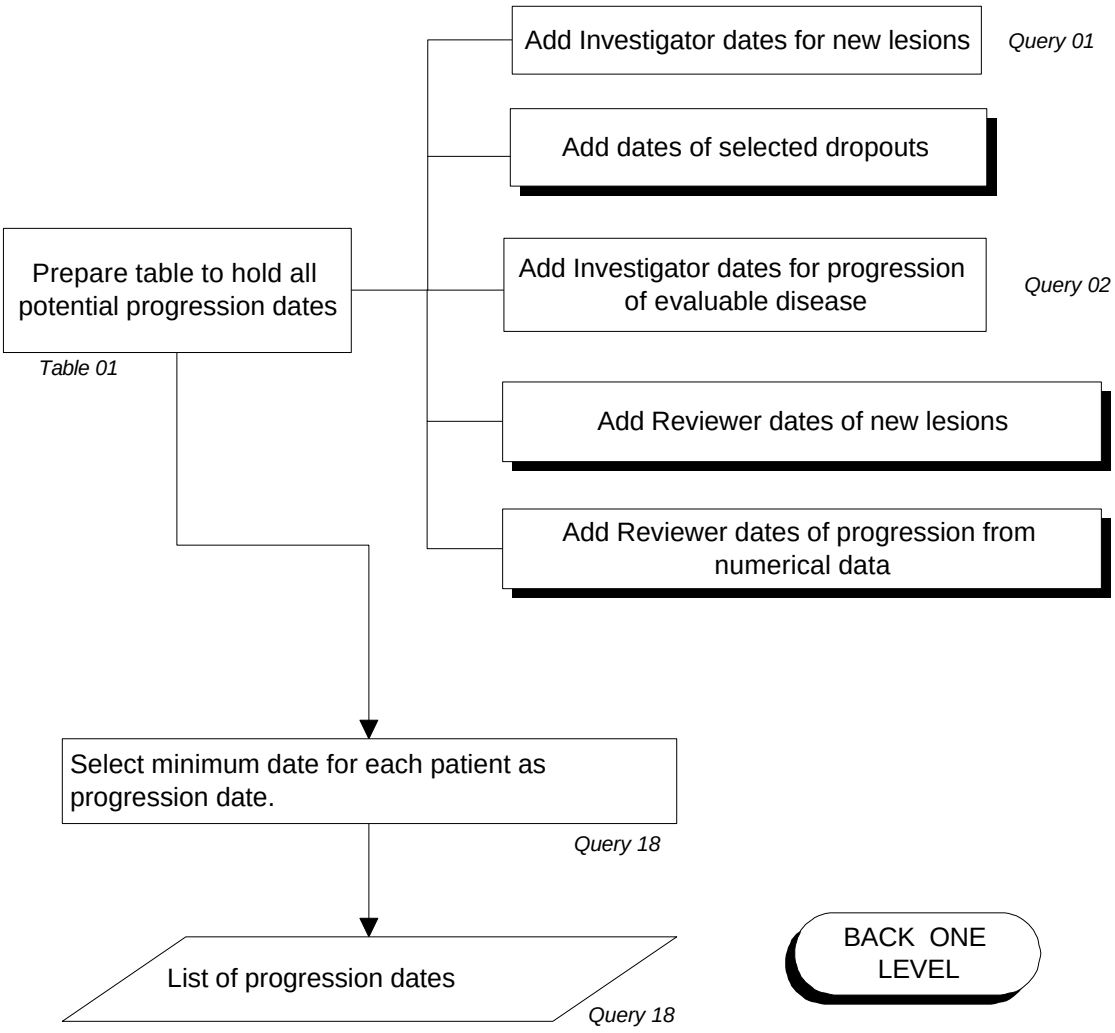


*See 'numerical measurements data table'

BACK ONE LEVEL

C:\$CREATIV\Progress\Link5.abc

Progression Dates



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Adding Dates of Selected Dropouts

-Informative censoring, i.e. censoring which is related in some way to impending progression, can confound the analysis.

-One may decide that some or all dropouts should be counted as progression in the primary analysis. An example would be dropouts for death or severe toxicity.

-Another approach is to do both analyses, including and excluding dropout as progression, to assess the robustness of the time to progression findings.

BACK ONE LEVEL

C:\$CREATIV\Progress\Link6.abc

New Lesions

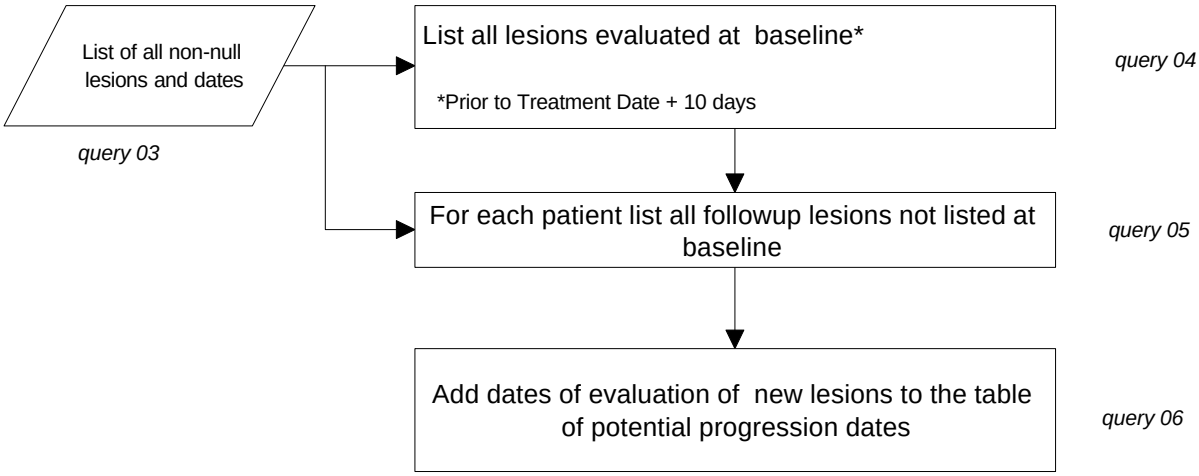


Table 01

BACK ONE LEVEL

C:\$CREATIV\Progress\Link7.abc

Reviewer dates of progression from numerical data

For Progression defined as increase of 25% in any lesion from nadir, calculated by the Method of Doublets

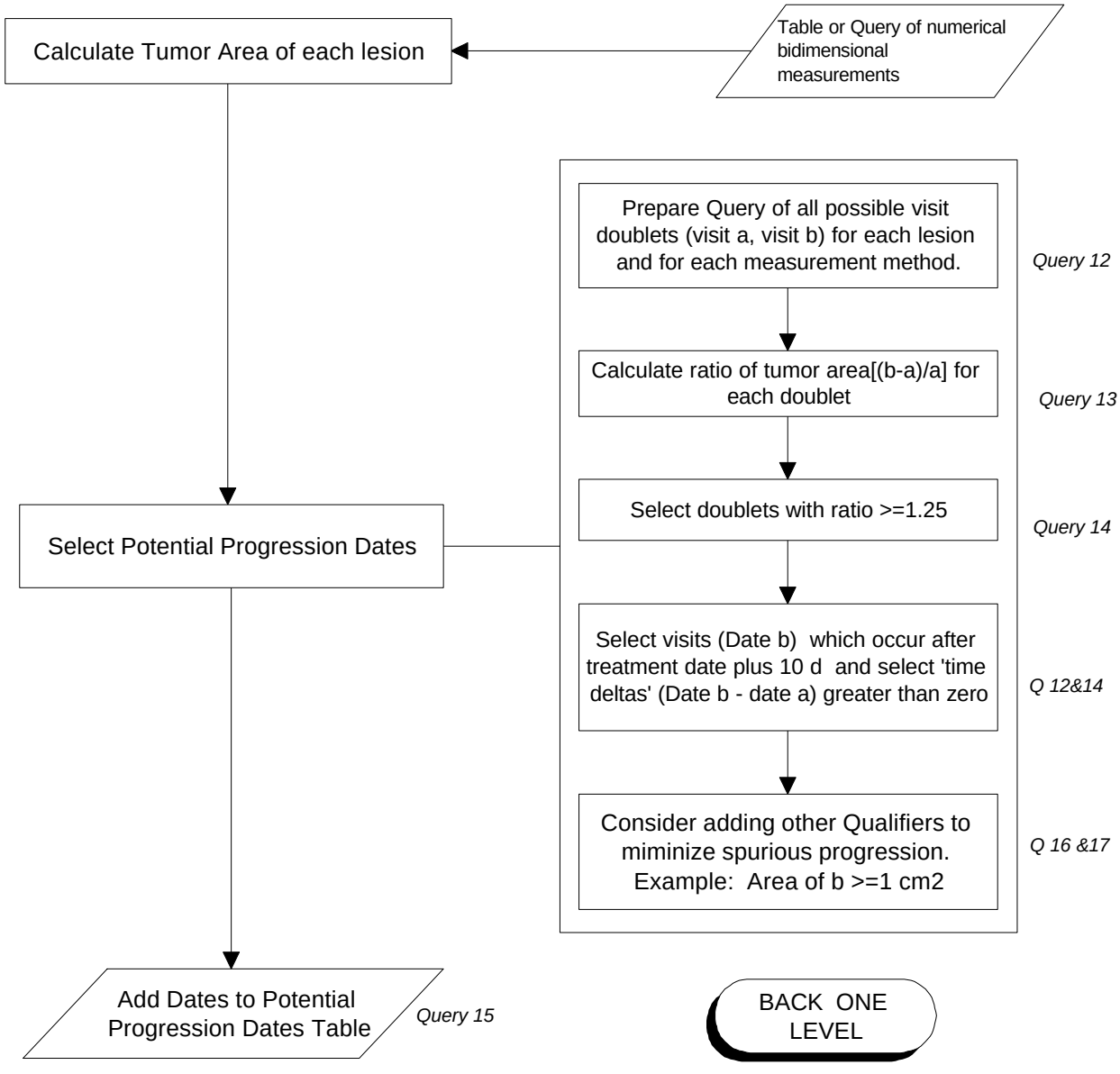
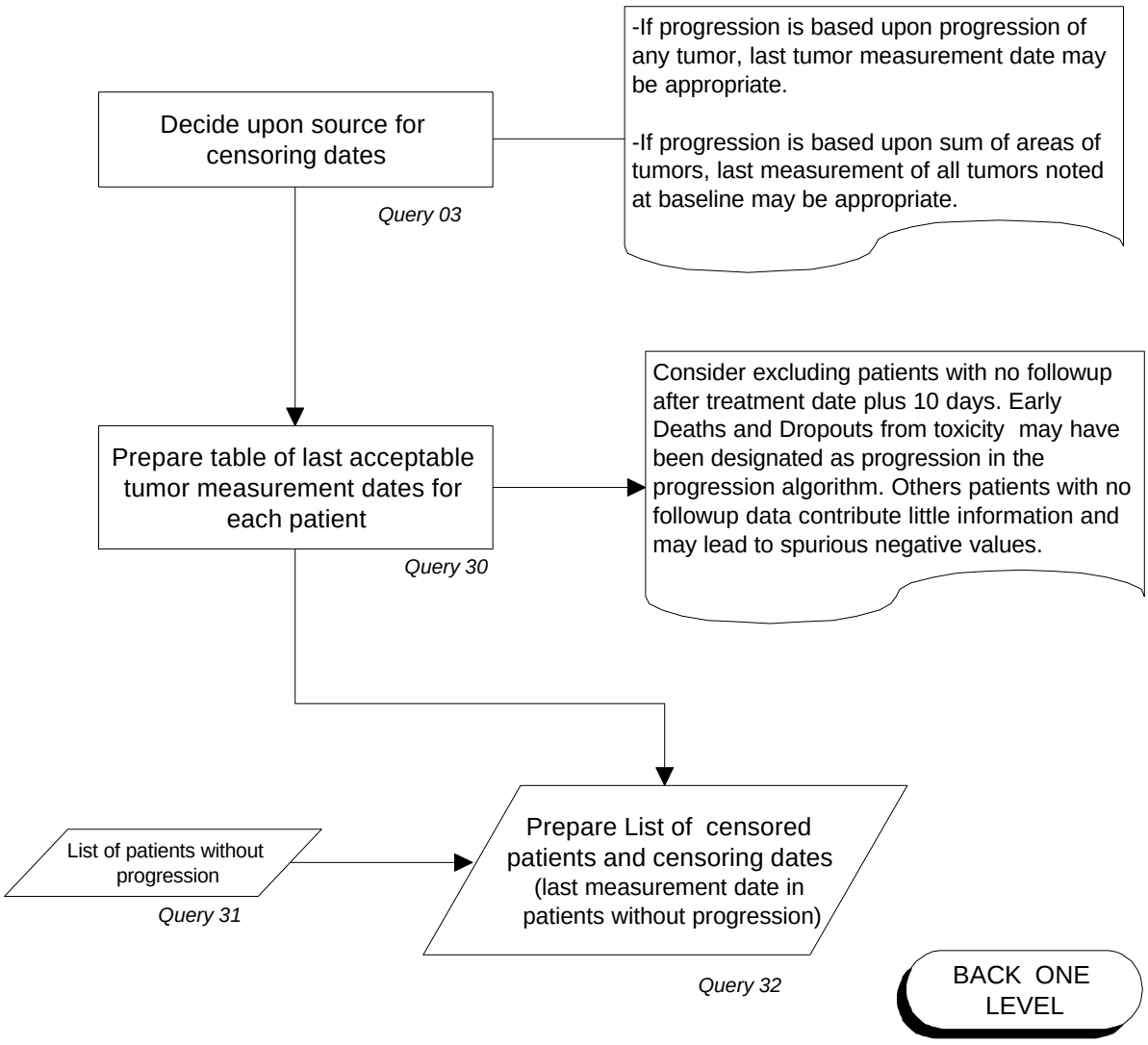


Table 01

C:\$CREATIV\Progress\link8.abc

Establish Censoring Dates



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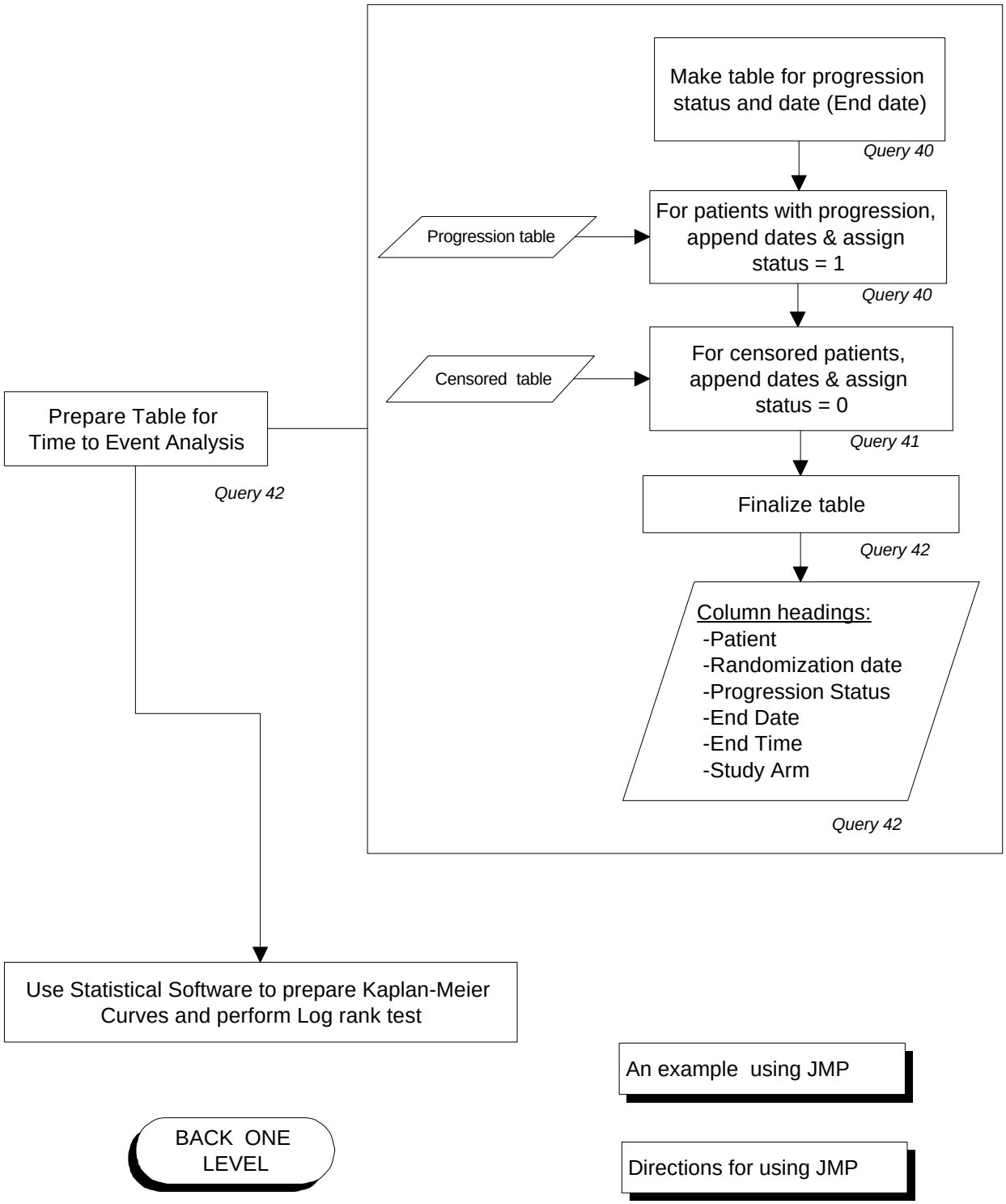
Calculate and Graph Time to Progression



Using JMP to do a survival (time to event) analysis

Verify that your PC is connected to the division W Drive or map this option in "my computer" on your desktop. The drive path is \\CDV017\DOPDPAPP. In Windows 95 explorer, find JMP.EXE file in the JMP directory and drag the icon to your desktop.

Time to Event Analyses in JMP from data generated in MSACCESS

1. Export query or table from ACCESS as 'text delimited'data. Select the option "store field names in first row" , select options in dialogue box, and choose 'tab' as field separator (this may be the default).

2. In JMP, import the file as a text file. In the dialogue box select 'tab' as end of field and select 'label' to import the label names from the first row of the data. Choose 'Survival' from the analysis window. Choose Kaplan-Meier method.

3. In the dialogue box match up each data label with the appropriate label in JMP: Select treatment arm and match it to GROUPING, select censoring status and match it to CENSOR, and select survival time and match it to TIME. When using JMP, it is important to note that the survival data must be prepared so that a a '1' corresponds to censoring while a '0' corresponds to a non-censored event such as death.

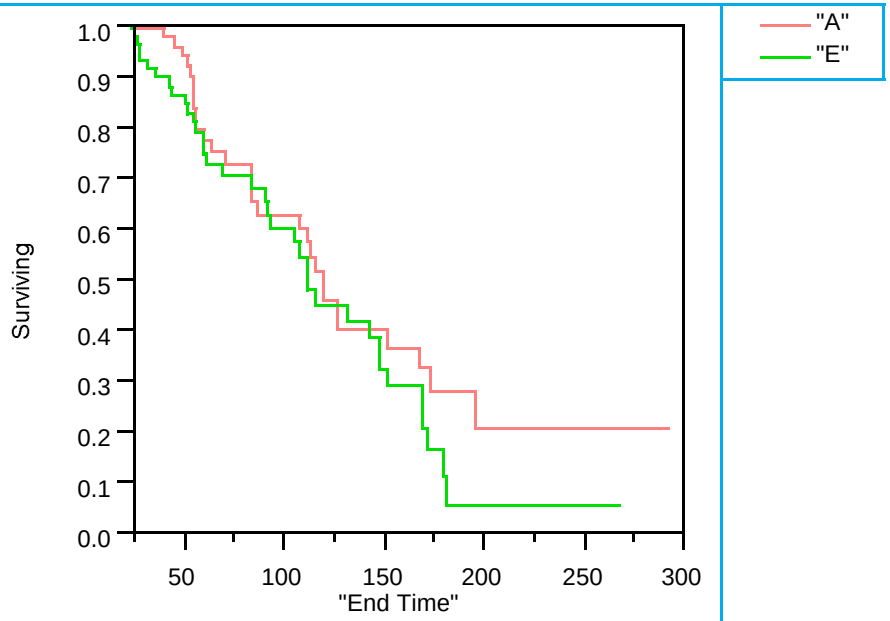
4. Select OK. A KM curve with log rank and Wilcoxon tests will be generated. Median values can be determined by from the listed data. I verified the results with the Companies value and with SPSS using the same survival data set.

5. While JMP does not appear to generate a median value; this can be obtained by examining the data tables. Look down the 'Survival' column and find the first number below 0.50. The survival time of this record appears to be the median (verified with 2 different survival data sets using SPSS).

BACK ONE LEVEL

Product-Limit Survival Estimates
Time Variable: "End Time"
Censoring Variable: "JMPSTATUS"

Survival Plot



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	1.4429	1	0.2297
Wilcoxon	0.9044	1	0.3416

"A"

"End Time"	Survival	Failure	SurvStdErr	N Failed	N Censored	At Risk
0.000	1.0000	0.0000	0.0000	0	0	59
28.000	1.0000	0.0000	0.0000	0	1	59
29.000	1.0000	0.0000	0.0000	0	2	58
32.000	1.0000	0.0000	0.0000	0	1	56
36.000	1.0000	0.0000	0.0000	0	1	55
39.000	1.0000	0.0000	0.0000	0	1	54
41.000	0.9811	0.0189	0.0187	1	0	53
46.000	0.9623	0.0377	0.0262	1	0	52
50.000	0.9434	0.0566	0.0317	1	1	51
51.000	0.9434	0.0566	0.0317	0	1	49
52.000	0.9237	0.0763	0.0367	1	0	48
53.000	0.9237	0.0763	0.0367	0	2	47
54.000	0.9032	0.0968	0.0412	1	0	45
55.000	0.8416	0.1584	0.0515	3	0	44
56.000	0.8416	0.1584	0.0515	0	2	41
57.000	0.7985	0.2015	0.0572	2	1	39
59.000	0.7985	0.2015	0.0572	0	1	36
61.000	0.7757	0.2243	0.0599	1	0	35
65.000	0.7528	0.2472	0.0624	1	0	34
67.000	0.7528	0.2472	0.0624	0	1	33
71.000	0.7293	0.2707	0.0647	1	0	32
80.000	0.7293	0.2707	0.0647	0	1	31
82.000	0.7293	0.2707	0.0647	0	1	30
85.000	0.6539	0.3461	0.0712	3	1	29
87.000	0.6277	0.3723	0.0730	1	0	25
109.000	0.6016	0.3984	0.0745	1	1	24
113.000	0.5742	0.4258	0.0759	1	0	22
114.000	0.5469	0.4531	0.0771	1	0	21
116.000	0.5195	0.4805	0.0779	1	0	20
120.000	0.5195	0.4805	0.0779	0	1	19
121.000	0.4618	0.5382	0.0792	2	1	18
127.000	0.4002	0.5998	0.0797	2	0	15

"End Time"	Survival	Failure	SurvStdErr	N Failed	N Censored	At Risk
149.000	0.4002	0.5998	0.0797	0	2	13
152.000	0.3638	0.6362	0.0804	1	0	11
168.000	0.3275	0.6725	0.0801	1	0	10
169.000	0.3275	0.6725	0.0801	0	1	9
170.000	0.3275	0.6725	0.0801	0	1	8
174.000	0.2807	0.7193	0.0812	1	0	7
177.000	0.2807	0.7193	0.0812	0	1	6
185.000	0.2807	0.7193	0.0812	0	1	5
197.000	0.2105	0.7895	0.0860	1	0	4
203.000	0.2105	0.7895	0.0860	0	1	3
263.000	0.2105	0.7895	0.0860	0	1	2
292.000	0.2105	0.7895	0.0860	0	1	1

Mean[biased]	Std Dev
125.90744	8.8248493

"E"

"End Time"	Survival	Failure	SurvStdErr	N Failed	N Censored	At Risk
0.000	1.0000	0.0000	0.0000	0	0	62
25.000	0.9839	0.0161	0.0160	1	0	62
27.000	0.9677	0.0323	0.0224	1	0	61
28.000	0.9355	0.0645	0.0312	2	2	60
32.000	0.9188	0.0812	0.0348	1	1	56
35.000	0.9188	0.0812	0.0348	0	1	54
37.000	0.9014	0.0986	0.0382	1	0	53
43.000	0.8841	0.1159	0.0413	1	0	52
44.000	0.8668	0.1332	0.0439	1	0	51
50.000	0.8668	0.1332	0.0439	0	1	50
51.000	0.8491	0.1509	0.0465	1	0	49
53.000	0.8314	0.1686	0.0487	1	3	48
55.000	0.8125	0.1875	0.0512	1	1	44
56.000	0.7932	0.2068	0.0535	1	1	42
58.000	0.7932	0.2068	0.0535	0	1	40
60.000	0.7728	0.2272	0.0558	1	2	39
61.000	0.7513	0.2487	0.0583	1	1	36
62.000	0.7293	0.2707	0.0606	1	0	34
70.000	0.7072	0.2928	0.0627	1	0	33
80.000	0.7072	0.2928	0.0627	0	1	32
84.000	0.7072	0.2928	0.0627	0	1	31
85.000	0.6836	0.3164	0.0649	1	1	30
90.000	0.6836	0.3164	0.0649	0	2	28
91.000	0.6573	0.3427	0.0675	1	0	26
92.000	0.6310	0.3690	0.0697	1	0	25
94.000	0.6047	0.3953	0.0716	1	0	24
105.000	0.6047	0.3953	0.0716	0	1	23
106.000	0.5772	0.4228	0.0734	1	1	22
107.000	0.5772	0.4228	0.0734	0	1	20
109.000	0.5468	0.4532	0.0756	1	0	19
112.000	0.5165	0.4835	0.0773	1	1	18
113.000	0.4842	0.5158	0.0789	1	0	16

"End Time"	Survival	Failure	SurvStdErr	N Failed	N Censored	At Risk
116.000	0.4519	0.5481	0.0800	1	0	15
132.000	0.4196	0.5804	0.0805	1	0	14
143.000	0.3873	0.6127	0.0805	1	0	13
148.000	0.3228	0.6772	0.0790	2	0	12
152.000	0.2905	0.7095	0.0774	1	0	10
158.000	0.2905	0.7095	0.0774	0	1	9
162.000	0.2905	0.7095	0.0774	0	1	8
170.000	0.2075	0.7925	0.0743	2	0	7
172.000	0.1660	0.8340	0.0701	1	0	5
173.000	0.1660	0.8340	0.0701	0	1	4
180.000	0.1107	0.8893	0.0650	1	0	3
182.000	0.0553	0.9447	0.0509	1	0	2
268.000	0.0553	0.9447	0.0509	0	1	1

Mean[biased]	Std Dev
114.82911	7.7462509

Combined