



March 18, 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2012-D-1145; Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we provide these comments on the Food and Drug Administration (FDA) “Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products (hereinafter “guidance”).

AdvaMedDx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies in the United States and abroad. Our membership includes manufacturers engaged in the development of innovative diagnostics supporting the public health, including technologies used to support enrichment strategies for clinical trials in support of drug and biological product approval.

GENERAL COMMENTS

AdvaMedDx appreciates FDA (or “Agency”) efforts to develop this guidance, which covers several trial designs that may be useful in drug and biologic clinical trials and reflects FDA commitment to foster personalized medicine. As innovators in the field, we concur that diagnostic tests play a valuable role in enrichment strategy for trials to support drug and biologic product approval and targeted care for patients.

Diagnostic tests can improve the efficiency of drug and biologic trials and facilitate overall new product development and investment. As noted in the guidance, “[c]linical trials are not designed to demonstrate the effectiveness of a treatment in a random sample of the general population.” AdvaMedDx appreciates FDA’s recognition of the role of selection strategies where the effect of a drug can more readily be demonstrated. We note this guidance also fits well with recent FDA draft guidance specific to companion

diagnostic tests, which supports safe and effective use of therapeutic products, and we look forward to issuance of this final guidance as well as additional codevelopment guidance.

Similar to the current appendix that provides a helpful listing of additional related FDA guidances (e.g., FDA Draft Guidance on *In Vitro* Companion Diagnostic Devices or hereinafter “companion diagnostic guidance”), AdvaMedDx would recommend inclusion of a glossary of terms and associated regulatory definitions within the context of enrichment strategies to better understand FDA current thinking and expectations. Definitions would be helpful for key terms, such as classifier, biomarkers, validated assay, and companion diagnostics. Use of such terms should also be consistent throughout the document and should be similar, to the extent possible, with similar language and terminology that is found in the companion diagnostic guidance once final. Consistent use of diagnostic-related terminology in this and other guidance will improve clarity, aid in consistency with other guidance issued by the Agency, and support an overall transparent and risk-based regulatory framework.

In that vein, AdvaMedDx would also recommend a section (e.g., scope) to explain FDA’s use of and reasoning for the examples contained and clarify whether they are intended as purely illustrative or represent types of approaches that would be acceptable today. Without such clarification, the examples may be confusing in the context of FDA guidance and representation of its’ latest and current thinking in contrast to a white paper or other discussion document that might be developed by the FDA.

Lastly, we also believe the guidance is equally useful for FDA staff as well as industry. At present, the title appears to indicate its use limited to manufacturers, but this may be due to contained historical information or background which may have less relevance to the current regulatory framework. FDA may wish, however, to consider retitling the document.

AdvaMedDx recognizes that the guidance reflects tremendous effort and collaboration amongst the Centers and applauds the Agency for undertaking this effort. We greatly appreciate the opportunity to provide comment. We have also included specific comments with accompanying recommendations. We hope our comments are useful as FDA moves to issue final guidance. AdvaMedDx would also welcome additional dialogue to discuss emerging scientific and technical issues regarding companion development of drugs and diagnostics (e.g., future roundtable).

If you have any questions, please do not hesitate to contact me at 202-434-7267 or by email at kcalleja@advamed.org.

SPECIFIC COMMENTS

AdvaMedDx's specific comments on the draft guidance follow and provide more detailed recommendations and some points for additional clarification.

Sincerely,

/s/

Khatereh Calleja
Vice President
Technology and Regulatory Affairs

ADVAMEDDX SPECIFIC COMMENTS

AdvaMedDx Comments on Draft Guidance for Industry—
Enrichment Strategies for Clinical Trials to Support Approval of Human Drug and Biological Products

Edit No. – Comment number

Change – Proposed change to the guidance

Section –Section of the guidance

Comment/Rationale – Reason for proposed change

Line No. – Guidance line number

Edit No.	Section	Line No.	Change	Comment/Rationale
1	General		The document could be improved by more consistent attention to the question of whether or not and when a diagnostic assay for a biomarker—when used as an enrichment classifier/tool—will be required to be approved as an <i>in vitro</i> diagnostic test (IVD) or companion diagnostic (CoDx) at the time of drug approval.	This is a key question in the use of biomarkers for enrichment.
2	Various Sections	199-304, 309-337, 427-475, 514-628, 690-	Provide an introductory statement (e.g., scope) explaining FDA’s purpose for including all the historical examples. Clarify whether they are intended as purely illustrative or represent types of approaches that would be acceptable today. For each example, also explain whether or not the same approach would be acceptable in today’s regulatory environment and discuss any modifications to the approach that would be necessary (i.e., implications for labeling, CoDx	As discussed, the guidance reads more like a whitepaper in various sections rather than a guidance reflecting FDA latest thinking based on the current regulatory environment. While such information can be useful, further explanation is needed for understanding of FDA expectation. It is unclear if the enrichment strategies in the examples are still valid. It is also unclear whether the guidance can be

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		705, 731-777, and 811-894	approval, expected assay performance information). If an example includes a CoDx, identify it as a CoDx. It may be worthwhile to consider placing the historical examples into an appendix and reducing the corresponding number and detail.	generally applied to approval pathways going forward. The examples are better fit for an appendix to allow for a more focused FDA regulatory guidance. The main body of the guidance should contain key recommendations/strategies and less historical background.
3	Background II.	62-66	Create an additional strategy on “reducing placebo effect.”	The enrichment strategy to decrease heterogeneity includes an approach to exclude patients likely to have high placebo effect. This approach affects not only variability, but it also affects the expected treatment effect – such that it may not lead to reducing variability.
4	Background II.	67-70	Include other types of responses (e.g., ordinal, counts) in the guidance and when possible explain why prognostic enrichment strategies can only increase the absolute effect difference but not the relative effect.	The discussion of prognostic strategy implies that there could only be two types of endpoints: events (binary endpoint) and continuous responses.
5	Background II.	73-77	Further explain why predictive enrichment would lead to both relative and absolute increases in effect size and why this differentiation between the two types of enrichment is relevant.	The guidance states that choosing patients more likely to respond to the drug can lead to a larger effect size, both absolute and relative.

Edit No.	Section	Line No.	Change	Comment/Rationale
6	Background II.	96	Introduce the use of diagnostic assays as enrichment tools earlier in the document.	This is a key topic and should be brought into the introductory sections of the document.
7	Decreasing Heterogeneity III.	99 - 167	Consider shortening or eliminating this section. Alternatively, retain bullets but eliminate paragraphs A and B.	This is standard information for clinical study design, generally known, and not necessarily needed for this document.
8	Prognostic Enrichment Strategies IV.	168	<p>Clarify that for purposes of prognostic enrichment strategies, high-risk patients are not always those who are already in a late stage of the disease.</p> <p>Also clarify the burden of proof on the “prognostic indicators” to allow a healthy “at risk” patient to be included in a drug trial.</p>	Additional clarity is needed. This paragraph seems to put emphasis on only serious events (i.e., rate of death) which could make such a strategy only valuable for long-term trials.
9	Prognostic Enrichment Strategies IV.	243	Consider changing “chemoprevention” to “preventative therapy.”	Use of a more generic term is more all-encompassing. For example, tamoxifen is not strictly chemotherapy, but it is rather a hormone therapy.
10	Predictive Enrichment V.	327	<p>Add the following sentence after “...controlled study.”:</p> <p>“Use of well characterized <i>in vitro</i> diagnostic markers with high negative or positive predictive performance should be considered.”</p>	Diagnostics assays would be a useful tool here.

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11	Predictive Enrichment V.	354	Add the following sentence at the end of the paragraph: “The use of an enriched population in a clinical trial may require the use of an existing or contemporaneously developed companion diagnostic test.”	The document could benefit from more clarification regarding when a CoDx is necessary.
12	Predictive Enrichment V.	358	Should read “Table 1” not “Table 2”	This appears to be a typo.
13	Predictive Enrichment V.	374	Add the following sentence: “The inclusion of a marker-selected population may require the use of an existing or contemporaneously developed companion diagnostic test.”	The document could benefit from more clarification regarding when a CoDx is necessary.
14	Predictive Enrichment V.	381	Identification of a responder population may require the use of an existing or contemporaneously developed companion diagnostic test.	The document could benefit from more clarification regarding when a CoDx is necessary.
15	Predictive Enrichment V.	401	Provide example in which a strong mechanistic rationale might demonstrate the need that non-responders do not need to be studied.	There is supportive literature, particularly in oncology, which supports this notion. This is likely to be representative with other targeted therapies.
16	Predictive Enrichment	408	Add the following sentence: “In any case, the study design should aim to	This is important to be able to make statistically valid conclusions.

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	V.		ensure, that the prevalence of marker-positive individuals in the control and treatment arm are equivalent.”	
17	Predictive Enrichment V.	499-500	Clarify the scope to which information about a patient’s response to a treatment class would apply.	It is unclear whether the information about a patient’s response to a treatment class would only apply to “me-too” compounds.
18	Predictive Enrichment V.	544-556	Add to the example that CYP2D6 polymorphisms have been used as a predictor of outcome in breast cancer patients treated with tamoxifen. See as an example Clin Cancer Res. 2010 Sep 1;16(17):4468-77. doi: 10.1158/1078-0432.CCR-10-0478. Epub 2010 Jun 1. CYP2D6 polymorphisms as predictors of outcome in breast cancer patients treated with tamoxifen: expanded polymorphism coverage improves risk stratification. <u>Schroth W, Hamann U, Fasching PA, Dauser S, Winter S, Eichelbaum M, Schwab M, Brauch H.</u>	We appreciate FDA’s example that employs “Metabolism of the Test Drug” among the pathophysiological strategies to enable better selection of patients and suggest this additional helpful example be added to the discussion of such strategies.
19	Various Sections	630-633, 927-931, 1210-1213, et. al.	We recommend that FDA adopt in this guidance language similar to that in its draft guidance on <i>in vitro</i> companion diagnostic devices. Specifically, it would be helpful if FDA would provide a much clearer statement that tests for markers and other classifiers be studied in a manner with appropriate study oversight (e.g., IND or IDE) for Phase III clinical studies. In addition, it is important to	Consistent with the Agency’s draft companion diagnostic guidance, we concur that cleared or approved companion diagnostics can be critical in supporting therapeutic discovery and safe and effective use of therapeutics. In contrast, tests with inadequate analytical or clinical performance or other issues related to safety and effectiveness may have serious

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			<p>note that the development and approval timeline may not, however, always mesh ideally (i.e., contemporaneous development and approval/clearance may not be feasible).</p>	<p>health consequences (i.e., withholding an appropriate therapy or administering an inappropriate therapy). AdvaMedDx has long supported a risk-based approach to the regulation of all diagnostic tests—whether developed by manufacturers or clinical laboratories—based on the risk associated with the use of the results in patient management. Such an approach is not only essential to assuring patient access to all safe and effective diagnostic technologies, but to moving toward full realization of personalized medicine.</p> <p>As FDA states in the draft companion diagnostic guidance:</p> <p>“FDA believes that use of an IVD companion diagnostic device with a therapeutic product raises important concerns about the safety and effectiveness of both the IVD companion diagnostic device and the therapeutic product. Because an IVD companion diagnostic device with inadequate ‘performance characteristics’ or other issues related to safety and effectiveness could expose a patient to preventable treatment risks, FDA will assess the safety and effectiveness of the IVD companion diagnostic device as used with the therapeutic, when a</p>

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				<p>therapeutic product depends on the IVD companion diagnostic device for its safe and effective use.”</p> <p>In addition, once the therapeutic is approved, FDA provides that it may only be labeled for use with an FDA-approved or cleared diagnostic.</p> <p>Such addition is important for consistency with previously issued guidance and to support patient care.</p>
20	Predictive Enrichment V.	630-633	<p>Clarify that data may simply not exist in early clinical trials for measuring sensitivity, specificity, and predictive value of novel markers intended for therapeutic efficacy.</p> <p>Clarify FDA means analytical sensitivity and specificity.</p> <p>The term “as much information as possible” is also very vague and should be revised.</p>	<p>In early studies, the lower number of clinical samples may be too small to have meaningful measurements.</p> <p>We assume that FDA means analytical (rather than clinical) sensitivity and specificity.</p> <p>More precise guidance would be helpful to understand the level of evidence needed for the selection classifier/ biomarker.</p>
21	Predictive Enrichment V.	655-692	<p>Clarify that the comments and statistical approaches in this section are applicable for other kinds of enrichment biomarkers—not just genomic subsets. Perhaps this could be clarified in a footnote.</p>	<p>These strategies should not be limited to genomic markers.</p> <p>We appreciate inclusion of the statistical approaches; however, they can be</p>

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			<p>Specifically clarify whether these statistical approaches can be used in a pivotal drug study; and if so, whether they will suffice for approval of the drug and /or an associated diagnostic IVD.</p> <p>Include in this portion or Section VII a discussion of practical regulatory details for how to implement some of these approaches where the marker/cut-off is not known prospectively.</p>	<p>interpreted to be contrary to standard advice for getting an IVD approved (i.e., separate studies to identify a cut-off and validate the cut-off) and it would be helpful to have this point addressed clearly.</p>
22	Predictive Enrichment V.	688	<p>Consider adding an example around sequential unblinding of similarly-designed pivotal studies. In this approach after the first unblended study is shown to meet its primary pre-specified endpoint, the cut-off could be refined. The refined cut-off could then be used to analyze the second unblended study. This approach would allow identification of a potentially better cut-off and appropriately preserve Type I error.</p>	<p>This is a logical extension of the approaches described.</p>
23	Predictive Enrichment V.	779	<p>Clarify by adding some text to separate these concepts.</p>	<p>The enrichment strategies discussed refer to specific methodologies used to identify a sub-population likely to have a greater response to treatment than the general population. This section does not, however, seem to be just for an enrichment strategy. Studies using such patients are intended to address an unmet medical need,</p>

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				<p>and do so by assessing whether a new therapy offers a better therapeutic effect than the currently available therapies. Such studies do not necessarily provide answers to questions related to treatment effect in the general population.</p>
24	Predictive Enrichment V.	808-809	Explain more what would be needed to establish overall superiority of a new drug.	The note refers to two approaches for using studies in non-responders or patients intolerant of other therapy and discusses how an effect may be demonstrated. Lines 798-799 discuss demonstration of a treatment effect that is “moderately superior” yet the note says that neither approach would establish overall superiority of the new drug.
25	Enrichment Study Design and Other Considerations VI.	900-901	Provide guidance on whether the utility of the companion diagnostic should be included in a multiplicity adjustment.	Potential multiplicity issues often arise in simultaneous development of a new drug with a companion diagnostic for identification of patients who are likely to benefit from the drug. While the primary objective of such a study is usually to demonstrate efficacy in a specific patient sub-population, guidance would be helpful on whether the utility of the companion diagnostic should be included in a multiplicity adjustment.

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26	Enrichment Study Design and Other Considerations VI.	919	Add “negative and positive predictive value” to the brackets (sensitivity, specificity). Also clarify whether analytical or clinical sensitivity or specificity is meant.	These are important performance characteristics. Diagnostic manufacturers would appreciate this level of clarity.
27	Enrichment Study Design and Other Considerations VI.	925	Clarify expectations when there is not a comparator or gold standard. Consider noting that in the absence of a comparator or gold standard test, the accuracy of a CoDx test may be based on clinical outcome.	This situation is not uncommon and an unambiguous statement would reduce confusion.
28	Enrichment Study Design and Other Considerations VI.	927	Add after “performance characteristics” the following: “including the lot to lot reproducibility”	This is an important performance characteristic.
29	Enrichment Study Design and Other Considerations VI.	937	Clarify this provision.	The statement about planned interim evaluations needs elaboration and is potentially confusing as written.
30	Enrichment Study Design and Other Considerations VI.	954	The discussion regarding exploring a range of threshold values needs more detail. Please reference this concept back to the study alpha discussion on page 16 (lines 655- 671) and elaborate with some practical regulatory advice on how the cut-off for a diagnostic could be both established and clinically validated using	This approach is currently contrary to standard advice for getting an IVD approved (e.g., perform separate studies to identify a cut-off and validate the cut-off). It would be helpful to have this point addressed clearly. The possibility for the cut-off to be adjusted or refined using the

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			only one Phase 3 study (e.g., use of pre-specified SAPS).	Phase 3 study can provide for possible needed flexibility with assuring safety and effectiveness.
31	Enrichment Study Design and Other Considerations VI.	962-1125	For each study design in this section, it would be helpful to state whether or not this study design would result in the need for an approved IVD and/or CoDx. If the decision about a CoDx must be made on individual basis for certain study designs, state so and list criteria that can impact the decision.	This is a key question in the use of biomarkers for enrichment.
32	Enrichment Study Design and Other Considerations VI.	1007-1010	Consider that a marker-positive only approach is appropriate in order to make a rapid assessment of activity or not in a small patient population.	This considers the risk of missing a signal of activity by not selecting patients, when a marker-positive population is a small fraction of the total, and the marker-negative population is not likely to respond.
33	Enrichment Study Design and Other Considerations VI.	1013	Add the following sentence: “If the companion diagnostic test is a quantitative method using a concentration cut-off to assign a positive or negative result, this study with only marker-positive individuals requires a separate validation of the cut-off definition of the test method. The cut-off used to assign the test positive versus negative status should be appropriately validated in a separate study. This is especially important for a quantitative, continuous marker	This will serve as an important reminder for development of a test for this use.

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			where the cut-off is based on a concentration and not a more qualitative measure such as presence/absence of a mutation.”	
34	Enrichment Study Design and Other Considerations VI.	1031	Replace “laboratory” with “diagnostic” or “ <i>in-vitro</i> diagnostic.” Also consider the scenario where an IVD is not yet ready at the time of product approval.	This will avoid any confusion and assure consistent language in the document. While the guidance indicates that an enrichment marker could be measured after drug approval using an established FDA-approved diagnostic test as a CoDx, it is possible that such an IVD is not yet ready at the time of product approval. Please consider this scenario and include it as a part of this guidance. While FDA importantly recognizes the value of such tests being developed and approved or cleared contemporaneously to support safe and effective use of therapeutic products, contemporaneous development may not always be possible (i.e., contemporaneous development and approval/clearance may not be feasible based on circumstances of the drug approval). For example, the clinical validation of a biomarker may take place late into phase 3 clinical trials during the New Drug Application filing period. We appreciate FDA flexibility so as not to deny approval of therapeutic product in the case when the companion diagnostic has not yet been approved or cleared. Such

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				scenario should likely involve a post-market commitment to obtain post-approval clearance or approval for the companion diagnostic once it is ready. In turn, FDA should expeditiously clear or approve such diagnostic tests.
35	Enrichment Study Design and Other Considerations VI.	1035-1082	Clarify for these examples when IDE approval by FDA would be required. Also add a statement addressing the situation where the overall response is positive, but a subpopulation shows an even greater benefit. This is not specifically addressed in this section. Indicate if a marker used in this situation would be a CoDx and/or an IVD for aimed contemporaneous approval with the therapeutic.	This clarification would be helpful along with necessary flexibility, consistent with previous AdvaMedDx comments on the draft companion diagnostic guidance. This is an unclear situation that is reasonably likely to occur. Clear guidance would be appreciated.
36	Enrichment Study Design and Other Considerations VI.	1034 – 1062, 1303-1369	We appreciate the statement that studies do not need to be designed to provide a definitive answer on the effect size in marker-negative patients. The summary of information necessary for marker-negative patients is generally helpful, but it is still unclear on a practical level what needs to be shown prior to a proposed marker-positive-only study to show that marker-negative patients would not benefit.	More specific advice would be appreciated. It would be helpful to understand the level of prior evidence required in order to support a marker-positive only study design.

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37	Enrichment Study Design and Other Considerations VI.	1039	Add to end of sentence “or there is significant risk to patient safety.”	This is an important consideration for patient safety.
38	Enrichment Study Design and Other Considerations VI.	1062	Revise to clarify that the randomization between marker-positive and marker-negative patients can be uneven, especially if treatment effect is expected to be small in the marker-negative patients.	Randomization between marker-positive and marker-negative patients is not necessarily 1:1.
39	Enrichment Study Design and Other Considerations VI.	1070-1082	<p>More clearly explain why test approval would not be necessary in this special situation, even if the drug only works in the marker-positive subset.</p> <p>Consider replacement of “approval of the test prior to approval of the drug” with “contemporaneous approval would not be required.”</p>	<p>Without clearer explanation, the discussion in this situation where the drug only works in the marker-positive subset seems inconsistent. Simply because you commence a therapeutic prior to receipt of a test result does not mean a clinician would not discontinue the drug once they know it would not work. The language is somewhat confusing.</p> <p>The “prior approval” wording is also confusing. There is no scenario for which a diagnostic must be approved before the drug, but rather contemporaneous approval is the goal.</p>

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40		1163-1164	Employing an adaptive enrichment study is supported. We strongly encourage further exploration and support by FDA.	FDA should seek new regulatory models and adaptive clinical trial designs to support product innovation for patients, including device development. There are limited case studies to date.
41		1175-1180	The idea of modifying the cut-off during the course of the study in order to increase the response rate is worth further exploration and should be expanded.	This is a good example of a discussion topic that is ripe for industry-FDA discussion. We have hosted this type of constructive discussion with FDA at previous roundtable events.
42	Enrichment Study Design and Other Considerations VI.	1181	Elaborate when it is acceptable to change the cut-off without comprising study integrity.	Similar to the preceding comment, this type of approach merits further discussion with FDA. Further clarity is appreciated as this could facilitate the process.
43	Enrichment Study Design and Other Considerations VI.	1200-1230	In this section (or elsewhere in the document), please clarify how enrichment strategies may be agreed upon so as to avoid bias in the intended use population.	Clarification would be helpful for better understanding of FDA expectations.
44	Enrichment – Regulatory Issues VII.	1210-1219	Consider revising.	It may be difficult to establish performance factors including sensitivity, specificity, and positive/negative predictive value prior to early clinical studies for markers of efficacy. In the case of a new or novel marker, this may not be possible due to the lack of a “gold standard” for comparison.

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45	Enrichment – Regulatory Issues VII.	1233- 1301	Clarify whether a sponsor will need to define or prove which category they are in and the case where some studies may be in-between or both.	While categories of enrichment are defined (lines 66-67) and examples are given, it would be helpful for the guidance to clarify implications of each category.
46	Enrichment – Regulatory Issues VII.	1244	Consider the following additional critical considerations when contemplating the use of enrichment designs in this regulatory issues section. First, consider necessity for bridging studies. In some cases, the diagnostic test utilized for enrichment during therapeutic trials (or ‘clinical trial test’) may not be ideal or practical for use in the real-world clinical setting. Also, additional IVDs are developed with the same intended use. Bridging studies may be acceptable in these types of situations.	The diagnostic test for an identified biomarker is not always available in final form until late in development of the drug. Also if there are any changes needed to the diagnostic during or after late clinical development of the drug, bridging studies may be needed.
47	Enrichment – Regulatory Issues VII.	1282- 1285	Revise or clarify the following statement: “...it seems clear that a drug shown effective in an enriched study should be available even if the responder population is not identified as precisely as would be desirable.”	Confusing statement that can be misunderstood. The document has reiterated the importance of the performance characteristics of the classifier test several times. Please reword or clarify.
48	Enrichment – Regulatory Issues VII.	1296- 1301 and 1377- 1378	We agree with FDA that evidence derived from studies using a solely enriched population can successfully support a drug approval; enrollment of biomarker-negative patients is not always necessary. In fact, it may not always be ethical.	This is a confusing statement that can be misunderstood.

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			<p>For that reason, we are concerned with the statement on line 1377 that “[i]f no marker-negative patients are studies, it will be difficult to describe the effect of enrichment fully.” Please reword or clarify.</p>	
49	Enrichment – Regulatory Issues VII.	1366	<p>Could the existence of an approved companion diagnostic be a requirement to collect less data in a marker-negative group?</p> <p>Consider adding existence of an approved companion diagnostic as a third bullet.</p>	<p>Presumably, the degree of efficacy (in a marker-negative group) may be a factor in setting the specification for the positive predictive value (PPV) of the diagnostic (more stringent if there is lack of benefit or harm in the marker-negative group).</p>
50	Enrichment – Regulatory Issues VII.	1372-1382 et. al.	<p>Expand this section as well as references to labeling throughout the document to summarize and clarify what section of the drug labeling specific kinds of “enrichment classifier” information belong. Also include information about what would be expected for any CoDx labeling and therapeutic labeling. Specifically discuss whether and when inclusion of biomarker-based classifier information in the drug labeling triggers the need for an approved or cleared CoDx. This can perhaps be added in a new section in VII.</p>	<p>This would aid clarity.</p>

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301- 827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
December 2012
Clinical Medical**

*Contains Nonbinding Recommendations
Draft – Not for Implementation*

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Center for Devices and Radiological Health (CDRH)**

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1
2
3 **Guidance for Industry¹**
4 **Enrichment Strategies for Clinical Trials to Support Approval of**
5 **Human Drug and Biological Products**
6

7
8 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
9 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind
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11 applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff
12 responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the
13 appropriate number listed on the title page of this guidance.
14

15
16
17 **I. INTRODUCTION**

18
19 This document provides guidance to industry on enrichment strategies that can be used in clinical trials
20 intended to support effectiveness and safety claims in new drug applications (NDAs) and biologics
21 license applications (BLAs). Similar strategies may also be useful in studies conducted in earlier
22 stages of development.

23
24 FDA's guidance documents, including this guidance, do not establish legally enforceable
25 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be
26 viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The
27 use of the word *should* in FDA guidances means that something is suggested or recommended, but not
28 required.
29

30
31 **II. BACKGROUND**

32
33 Clinical trials are not designed to demonstrate the effectiveness of a treatment in a random sample of
34 the general population. Instead, sponsors use a variety of strategies to select a subset of the general
35 population in which the effect of a drug, if there is one, can more readily be demonstrated. Some of
36 these selection strategies are obvious (e.g., patients are enrolled only if they have the disease that the
37 drug being studied is intended to treat), but there are many more ways in which patients are typically
38 chosen to make detection of a treatment effect more likely. Examples include selecting patients whose
39 disease does not spontaneously disappear or exhibit a large degree of variability, who are likely to
40 comply with treatment, who are likely to have a high rate of disease progression, or who have some

¹ This guidance was developed by the Center for Drug Evaluation and Research in coordination with the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health at the Food and Drug Administration.

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41 characteristic that suggests they can respond to the treatment. All of these selection strategies can be
42 described as *enrichment* of the study population.

43

For the purposes of this guidance, the term *enrichment* is defined as the prospective⁴⁴
use of any patient characteristic to select a study population in which detection of a⁴⁵
drug effect (if one is in fact present) is more likely than it would be in an unselected⁴⁶
population.⁴⁷

48

50
51 Among others, demographic, pathophysiologic, historical, genetic or proteomic, clinical, and
52 psychological characteristics have been used for enrichment. Enrichment may also refer to the
53 population to be analyzed within a broader population; that is, a study could include patients both with
54 and without the enrichment characteristic, but the primary analysis would be of the subset with the
55 characteristic, an approach that increases the study’s ability to detect a drug effect, but that can also
56 provide some information about patients without the enrichment characteristic. Although this guidance
57 focuses on enrichment directed at improving the ability of a study to detect a drug’s effectiveness,
58 similar strategies can be used in safety assessments.

59
60 Enrichment strategies fall into three broad categories:

- 61
- 62 1. *Strategies to decrease heterogeneity* – These include selecting patients with baseline
63 measurements in a narrow range (decreased inter-patient variability) and excluding patients
64 whose disease or symptoms improve spontaneously or whose measurements are highly
65 variable (decreased intra-patient variability). The decreased variability provided by these
66 strategies increases study power (see section III).
 - 67 2. *Prognostic enrichment strategies* – choosing patients with a greater likelihood of having a
68 disease-related endpoint event (for event-driven studies) or a substantial worsening in
69 condition (for continuous measurement endpoints) (section IV). These strategies will increase
70 the absolute effect difference between groups but will not alter relative effect.
 - 71 3. *Predictive enrichment strategies* – choosing patients more likely to respond to the drug
72 treatment than other patients with the condition being treated. Such selection can lead to a
73 larger effect size (both absolute and relative) and permit use of a smaller study population.
74 Selection of patients could be based on a specific aspect of a patient’s physiology or a disease
75 characteristic that is related in some manner to the study drug’s mechanism, or it could be
76 empiric (e.g., the patient has previously appeared to respond to a drug in the same class)
77 (section V).

78
79 This guidance describes and illustrates important enrichment strategies within these categories;
80 discusses study design options for different strategies, including advantages and disadvantages of the
81 various designs; and addresses issues of interpretation of the results of enrichment studies.

82
83 The enrichment strategies described in this guidance are discussed primarily in the context of
84 randomized controlled trials. In almost all cases, the strategies affect patient selection before
85 randomization (with a few exceptions for adaptive strategies to be noted later). These strategies,

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86 therefore, generally do not compromise the statistical validity of the trials or the meaningfulness of the
87 conclusions reached with respect to the population actually studied.
88

89 The principal concerns with the use of enrichment strategies relate to the generalizability and
90 applicability of the study results. When considering use of an enrichment design, it is important to
91 consider whether the enrichment strategy can be used in practice to identify the patients to whom the
92 drug should be given and whether the drug might be useful in a broader population than will be
93 studied. The extent to which patients who do not meet the selection criteria for enrichment should be
94 studied (section VII.B.) is therefore a critical consideration. In addition, the accuracy of the
95 measurements used to identify the enrichment population and the sensitivity and specificity of the
96 enrichment criterion in distinguishing responders and non-responders are also critical issues.

97
98

99 **III. DECREASING HETEROGENEITY**

100

101 Approaches to increasing study power – the ability of a clinical trial to demonstrate a treatment effect
102 if one is present – by decreasing heterogeneity (non-drug related variability) are widely practiced. The
103 following strategies are useful and generally accepted ways to decrease heterogeneity:
104

- 105 • Defining entry criteria carefully to ensure that entered patients actually have the disease that is
106 being studied and training investigators to adhere to protocol-specified entry definitions and
107 criteria.
- 108 • Identifying and selecting patients likely to comply with treatment to decrease variability in
109 drug exposure. *Note:* removing poor compliers identified after randomization is generally not
110 acceptable because such patients are not likely to be a random sample of the study population
111 and because compliance itself has been linked to outcome, even compliance in taking a
112 placebo.
- 113 • Using placebo-lead in periods prior to randomization to eliminate patients who improve
114 spontaneously or have large placebo responses.
- 115 • Decreasing intra-patient variability by enrolling only patients who give consistent baseline
116 values (e.g., for blood pressure measurements, treadmill exercise tests, pulmonary function
117 tests, or patient reported outcome (PRO) measures).
- 118 • Excluding patients taking drugs that are pharmacologically similar to, or that could interact
119 with, the study drug.
- 120 • Excluding patients unlikely to tolerate the drug.
- 121 • Excluding patients who are likely to drop out for non-medical reasons (e.g., because they have
122 difficulty getting to the study site).

123 Other strategies sometimes employed include eliminating patients in outcome trials with concomitant
124 illness likely to lead to early death or early drop-out and broad exclusions of patients on concomitant
125 therapies. There are concerns, however, that these strategies can result in studies that provide too little
126 information about the full range of people who will receive a drug in clinical practice, such as the
127 elderly, people with multiple illnesses, and those taking multiple drug therapies. It is not clear that

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128 concomitant illnesses that do not affect survival or other endpoint measurements or concomitant drugs
129 unrelated to a test drug really do interfere with assessment of a treatment effect. Therefore, the
130 implications of using these strategies should be carefully considered before they are used. Two of
131 these strategies – encouraging compliance and reducing the numbers of spontaneous improvers or
132 placebo responders – warrant further discussion (see below).

133

134 **A. Encouraging Compliance**

135

136 Practices such as encouraging good compliance by making patients aware of the conditions and
137 demands of the trial, avoiding too-rapid titration of drugs that could cause intolerable early side
138 effects, using adherence prompts and alert systems, and counting pills (or using “smart bottles” to
139 monitor drug use) so that non-compliant patients can be encouraged to perform better have become
140 standard. There have also, on occasion, been more specific efforts to identify and enroll good
141 compliers into clinical trials.

142

143 1. The VA Cooperative hypertension studies of the late 1960s and early 1970s^{2,3} gave prospective
144 patients placebo tablets containing riboflavin during a single-blind placebo period, then
145 examined patients’ urine for fluorescence and randomized only patients whose urine fluoresced
146 (evidence that the patients had been taking the riboflavin tablets) on two consecutive visits
147 during a 2-4 month observation period.

148 2. The Physicians’ Health Study⁴ used an 18-week, pre-randomization placebo run-in during which
149 patients (all physicians) self-reported compliance. About one third of the screened patients were
150 not randomized because of self-reported poor compliance. Compliance during the randomized
151 study was reported as a very satisfactory 90% over the 5 years of the study, greatly increasing its
152 power.⁵

153

154 **B. Decreasing Placebo Responses and Spontaneous Improvement**

155

156 In placebo-controlled trials of drugs for symptomatic conditions (e.g., depression, anxiety, angina) or
157 laboratory abnormalities (e.g., dyslipidemia, hypertension), it is relatively common to have a single-
158 blind, placebo lead-in period and to randomize only patients whose signs or symptoms remain above
159 some entry level value. This is in part to identify and not randomize patients who would have had an
160 improvement for a reason other than a response to the test treatment (spontaneous improvement, a
161 placebo response, or effect of expectations or observations) that resolved the patient’s symptoms or
162 signs, making the patient incapable of showing a response to treatment. Also, many signs and
163 symptoms vary spontaneously and, therefore, initial screening values that would support enrollment
164 may represent *random highs* of the disease course that will be followed by regression to the mean,
165 leaving the patient without the condition to be treated.

166

167

168 **IV. PROGNOSTIC ENRICHMENT STRATEGIES—IDENTIFYING HIGH-RISK**
169 **PATIENTS**

170

171 A wide variety of prognostic indicators have been used to identify patients with a greater likelihood of
172 having the event (or a large change in a continuous measure) of interest in a trial. These indications
173 include clinical and laboratory measures, medical history, and genomic or proteomic measures.

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174 Selecting such patients allows a treatment effect to be more readily discerned. For example, trials of
175 prevention strategies (reducing the rate of death or other serious event) in cardiovascular (CV) disease
176 are generally more successful if the patients enrolled have a high event rate, which will increase the
177 power of a study to detect any given level of risk reduction. Similarly, identification of patients at
178 high risk of a particular tumor, or at high risk of recurrence or metastatic disease can increase the
179 power of a study to detect an effect of a cancer treatment. Prognostic enrichment strategies are also
180 applicable, or potentially applicable, to the study of drugs intended to delay progression of a variety of
181 diseases, such as Alzheimer’s disease, Parkinson’s disease, rheumatoid arthritis, multiple sclerosis,
182 and other conditions, where patients with more rapid progression could be selected; it is possible, of
183 course, that such patients might be less responsive to treatment (i.e., that rapid progression would be a
184 negative predictor of response), and that would have to be considered.

185
186 For any given desired power in an event-based study, the appropriate sample size will depend on effect
187 size and the event rate in the placebo group. Prognostic enrichment does not increase the relative risk
188 reduction (e.g., percent of responders or percent improvement in a symptom), but will increase the
189 absolute effect size, generally allowing for a smaller sample size. For example, reduction of mortality
190 from 10% to 5% in a high-risk population is the same relative effect as a reduction from 1% to 0.5% in
191 a lower risk population, but a smaller sample size would be needed to show a 5% vs. 0.5% change in
192 absolute risk. It is common to choose patients at high risk for events for the initial outcome study of a
193 drug and, if successful, move on to larger studies in lower risk patients.

194
195 **A. Experience with Prognostic Enrichment Strategies**

196
197 *1. Cardiovascular Studies*

198
199 In CV disease, the severity of the illness being studied, as well as other factors that can indicate
200 increased risk, such as a history of recent myocardial infarction or stroke; the presence of concomitant
201 illness such as diabetes, hypertension, or hyperlipidemia; and certain blood markers, such as very high
202 LDL cholesterol, low HDL cholesterol and high C-reactive protein (CRP), have been used to identify
203 patients at greater risk for cardiovascular events, considerably reducing the sample sizes needed to
204 show an effect in outcome studies. Outcome studies using ACE inhibitors in congestive heart failure
205 (CHF) and HMG CoA reductase inhibitors in hyperlipidemia (the enalapril and statin trials,
206 respectively) illustrate this approach.

207
208 In the enalapril trials, mortality reduction and decreases in morbid events (such as hospitalization)
209 were first assessed in a very ill CHF population of NYHA Class IV patients (CONSENSUS),⁶ then in
210 less ill patients (SOLVD treatment⁷) and eventually in asymptomatic patients (SOLVD prevention⁸).
211 In the later studies, composite endpoints were needed because the number of early deaths was too low
212 to allow an effect to be demonstrated, about 15% at one year on placebo in SOLVD treatment and
213 about 5% in SOLVD prevention, far lower than the 44% placebo 6 month mortality in CONSENSUS.
214 The very high early mortality in CONSENSUS, together with the large effect size (40% reduction),
215 allowed demonstration of a survival effect in just 253 patients, while the studies in less ill patients
216 required studies of 2,000-4,000 patients. The higher risk patients enrolled as a result of prognostic
217 enrichment showed, as expected, a larger absolute effect size, but relative effect size was also greater
218 in the more ill patients, suggesting that severity was also a predictive marker (see section V).

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220 A similar strategy was used in the statin trials. The early CV outcome trials with statins were able to
221 evaluate the effects of the drugs on mortality because they enrolled patients with a history of heart
222 disease and very elevated cholesterol levels, patients whose mortality risk was substantial.^{9,10} As the
223 benefit of statins became established in high-risk patient populations, subsequent CV outcome trials
224 had to enroll patients with less marked LDL cholesterol elevations and without known coronary artery
225 disease – populations that had not yet been shown to benefit from LDL cholesterol lowering and who
226 could still be ethically studied, but who were identified as high risk because of some other illness (e.g.,
227 type 2 diabetes mellitus) or risk factor (e.g., low HDL cholesterol, elevated high-sensitivity CRP). As
228 the population's risk became lower, sample sizes increased considerably but prognostic factors made
229 the studies possible. For example, in the recent JUPITER study¹¹ (n=17,802), a statin was shown to
230 have an effect on outcome in patients with *normal* LDL cholesterol, but who were at higher CV risk
231 based on factors other than LDL cholesterol, including age, one additional CV risk factor, and a high-
232 sensitivity CRP ≥ 2 mg/L. As the magnitude of risk declined in these study populations, it often also
233 became necessary to rely on composite endpoints, as the mortality rate was too low to allow a
234 mortality trial of reasonable size.

235
236 Choosing patients at relatively high risk of cardiovascular events can also be critical to the success of
237 safety studies intended to rule out a given level of cardiovascular risk. This approach is now
238 recommended for new antidiabetic treatments¹² and has been a consideration in the design of studies to
239 evaluate the cardiovascular risk of non-steroidal anti-inflammatory drugs.

240
241 **2. Oncology**
242

243 It is clear that chemoprevention studies are most likely to be successful in people identified as high
244 risk (e.g., by genetic or other characteristics) for developing a cancer or recurrence of cancer. For
245 example, adjuvant therapy studies of tamoxifen showed that the drug not only delayed development of
246 metastases in patients with breast cancer, but also reduced the risk of contralateral tumors (new
247 primary tumors) in this high-risk group (high risk because they had already had breast cancer).
248 Tamoxifen was then studied in 13,000 high-risk people (calculated using the Gail model) without a
249 prior diagnosis of breast cancer who were followed for 4 years (NSABP P-1).¹³ The study showed a
250 44% relative reduction in risk of invasive breast cancer, and tamoxifen was labeled for use in reducing
251 the risk of breast cancer in high-risk individuals identified using the Gail model calculator. A study in
252 people at lower risk would have required a substantially larger sample size. For example, a study of
253 people with a risk that was 25% of the risk of the NSABP P-1 study population would have needed
254 about 20,000 people to detect an effect of the size observed in the NSABP P-1 study with 90% power.

255
256 **B. Potential Strategies for Prognostic Enrichment**
257

258 There may be additional approaches to identifying high-risk CV patients. A report in 2005¹⁴ pointed
259 out that a higher resting heart rate, a small increase in exercise heart rate, and delayed recovery of
260 heart rate were all strong predictors of sudden death, suggesting a potential enrichment strategy in
261 studies of drugs to prevent sudden death. More recently, the potential for risk prediction based on
262 genetic factors has been examined,¹⁵ as has the predictive value of coronary artery calcium score.^{16,17}
263 The actual usefulness of these potential predictors as enrichment tools has yet to be established.
264

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265 Published reports suggest additional strategies for identifying high-risk breast cancer patients,
266 especially for participation in studies of adjuvant treatment of cancer, where the likelihood of
267 recurrence and survival are critical to demonstrating an effect on these endpoints.
268

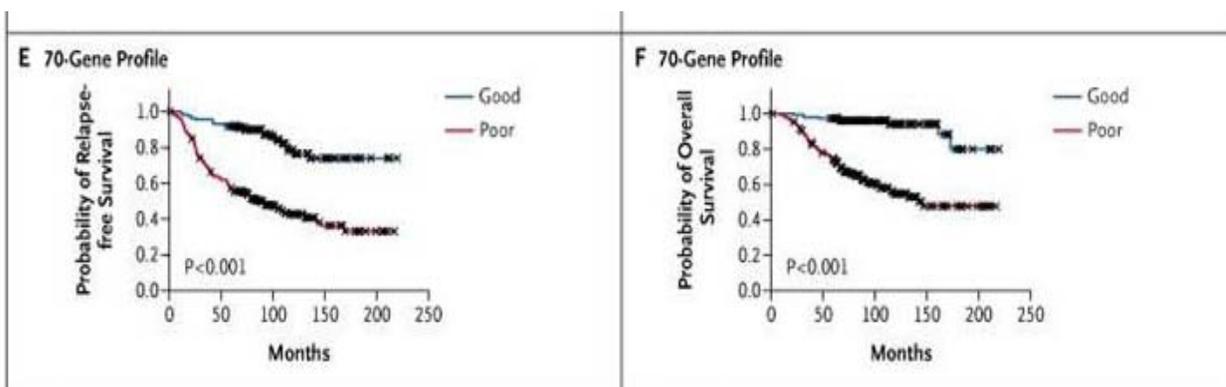
269 1. *Prostate Cancer*

270
271 It has been reported¹⁸ that in men with localized prostate cancer following radical prostatectomy, high
272 *PSA velocity* (PSA increase > 2 ng/mL during prior year) strongly predicted prostate cancer recurrence
273 and mortality over a 10-year period. Prognostic markers such as PSA velocity, if validated in future
274 studies, could be used to identify high-risk patients. Studies of adjuvant treatment for prostate cancer
275 would be better able to show an effect on survival if they enrolled patients with a high risk of death.
276

277 2. *Breast Cancer*

278
279 Many investigators have reported gene expression profiles that appeared to predict the likelihood of
280 breast cancer recurrence after surgery. Selection of a population with a high rate of recurrence and
281 poor survival is critical if an adjuvant therapy study is to be successful. In a report on the use of five
282 different gene-expression profiling approaches in a non-randomized 285-patient sample treated with
283 local therapy, tamoxifen, tamoxifen plus chemotherapy, or chemotherapy alone, Fan, et al.,¹⁹ found
284 that four of the five approaches for classifying patients had high concordance and a striking ability to
285 predict large differences in both recurrence and mortality, as illustrated in Figure 1, showing the
286 difference between patients with *good* and *poor* 70-gene profiles on relapse-free survival and overall
287 survival. These data need to be verified in actual trials, but gene expression profiling may provide a
288 means of identifying higher risk patients for adjuvant trials.
289

290 **Figure 1: Relapse Rates and Survival in Breast Cancer Patients Based on 70-Gene Profile**



292
293
294
295 Recently, MammaPrint, an in vitro diagnostic test using the gene expression profile of fresh breast
296 cancer tissue samples to assess a patient's risk for distant metastasis, was cleared by FDA as a
297 prognostic test for certain breast cancer patients. As noted, use of such a diagnostic test represents a
298 potential enrichment strategy for adjuvant trials to identify a population at higher risk for recurrence.
299

300 Women with a deleterious BRCA 1 or 2 mutation have a lifetime incidence of breast cancer and
301 ovarian cancer of 60% and 15-40%, respectively, compared to a risk of 12% and 1.4%, respectively, in

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302 women without a BRCA mutation.²⁰ Selecting women with such prognostic markers for a primary
303 prevention trial in breast cancer or ovarian cancer would increase the likelihood of cancer events,
304 thereby permitting a smaller sample size and a shorter study.

305
306

307 **V. PREDICTIVE ENRICHMENT**

308

309 There are many possible ways to identify patients more likely to respond to a particular intervention,
310 and these have long been used in clinical trials when selection of patients has been based on a specific
311 aspect of pathophysiology, past history of response, or a disease characteristic that is related in some
312 manner to the study drug's mechanism (e.g., genomic or proteomic factor). For example:

313

- 314 • CHF can result from either systolic or diastolic dysfunction. Presumably, a population with
315 systolic dysfunction would be more likely to respond in a study of an inotrope.
- 316 • High-renin status predicts a greater anti-hypertensive response to beta-blockers, ACE
317 inhibitors, and angiotensin receptor blockers. A population with high renin hypertension
318 would be more responsive than a general hypertension population in studies of drugs in these
319 classes.
- 320 • For some indications, antibacterial drug effects are best analyzed in patients whose organism is
321 sensitive to the antibacterial drug. Most commonly, patients are randomized before sensitivity
322 is known, but only those patients whose organism is subsequently found to be sensitive to the
323 test antibacterial are analyzed for effectiveness.
- 324 • An initial screening for response –a biomarker measurement (e.g., radiographic response or
325 reduction of ventricular premature beats), early clinical response, or full-fledged clinical
326 response – in an open pre-randomization period can be used to identify a responder population
327 to be randomized into the controlled study. This approach is of particular value when
328 responders constitute only a small fraction of the overall population to be treated.
- 329 • A population of non-responders, or people intolerant to another drug, can be randomized to the
330 new drug or the original drug. The comparison is enriched because the population is expected
331 to have a poor response or a high rate of intolerance to the original drug compared to the test
332 drug. These designs cannot be used where effectiveness is critical or the intolerance is
333 dangerous.
- 334 • Proteomic markers, such as the HER 2/neu marker in breast cancer indicating potential for
335 response to trastuzumab, tumor EGFR markers, or genetic markers related to a drug's
336 mechanism of action can be used to identify potential responders, a rapidly growing
337 enrichment strategy in oncology.

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338 Identifying a responder population (i.e., a subset of the overall population with a larger than average
 339 response to treatment) and studying this population in a clinical trial can provide two major
 340 advantages: increased study efficiency or feasibility and an enhanced benefit-risk relationship for the
 341 people in the subset compared to the overall population.

342
 343 *Increased Efficiency or Feasibility*
 344

345 Identification of a high treatment response population greatly increases the chance that a study of an
 346 effective drug will be able to detect a treatment effect and allows a study to succeed with a smaller
 347 sample size than a study in an unselected population. The strategy can be particularly useful for early
 348 effectiveness studies because it can provide clinical *proof of concept* and contribute to selection of
 349 appropriate doses for later studies. When the treatment responder population constitutes only a small
 350 fraction of all patients, say 20% (a common situation in oncology settings), enrichment can permit a
 351 showing of effectiveness when a study in an overall population may have difficulty showing any
 352 effect. Unlike prognostic enrichment, which leads to a larger absolute effect but no change in relative
 353 effect, a predictive enrichment population will show both a larger absolute effect and a larger relative
 354 effect than the general, unselected population.

355
 356 The extent to which the sample size needed to adequately power a study can be reduced using a
 357 predictive enrichment strategy is a function of the prevalence of the enrichment marker and the
 358 relative effectiveness of the drug in the marker-positive and marker-negative populations. Table 2
 359 illustrates how sample size ratios – the ratio of the number of subjects needed in an unselected
 360 population versus the number needed if only the marker positive population is studied – change with
 361 varying prevalence of marker-positive patients and different magnitudes of treatment effect in marker-
 362 negative patients (treatment effect in marker-negative patients of either 0% or 50% of the effect in
 363 marker-positives). Table 1 assumes the classification of patients into positive versus negative is 100%
 364 accurate.

365
 366 **Table 1: Sample Size Ratios as a Function of the Prevalence of Marker-Positive Patients**
 367

Prevalence of Marker-Positive Patients	Treatment Effect in Marker-Negative Patients (% of Marker-Positive Response)	
	0%	50%
	Sample Size Ratio	Sample Size Ratio
100%	1.0	1.0
75%	1.8	1.3
50%	4	1.8
25%	16	2.6

368
 369 In general, the lower the prevalence of marker-positive patients and the smaller the relative effect size
 370 in the marker-negative population, the more the sample size can be reduced in a study of marker-
 371 positive patients compared to a study in an unselected population. For example, when the prevalence
 372 of marker-positives in a population is only 25% and no treatment effect is expected in the 75% of

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373 patients who are marker-negative, the required sample size in a study of an unselected population
374 would be 16 times the sample size needed for a study that included only marker positive patients. A
375 more detailed description of these results and the conditions under which the results were obtained has
376 been presented by Simon and Maitournam.²¹

377
378 *Enhanced Benefit–Risk Relationship*

379
380 Identification of a responder population can enhance the benefit–risk relationship of a drug by
381 avoiding exposure and potential toxicity in people who cannot benefit from the drug. For drugs with
382 significant toxicity and a low overall response in a general population – factors that could deter further
383 development – identifying a responder population could make a risk more acceptable and facilitate
384 continued development and approval. For example, the significant survival advantage (approximately
385 5 months) seen with trastuzumab in the treatment of metastatic breast cancer in patients with high
386 HER 2/neu expressing tumors (about 25% of breast cancers) ultimately supported use of the drug in
387 the marker-selected population despite the significant cardiotoxicity that emerged (see further
388 discussion in section V.B.3). The much smaller mean effect (less than 2 months) that would have
389 been observed in an unselected population and the fact that only about one-fourth of patients would
390 have benefited might have made approval difficult to support in the face of the observed cardiotoxicity
391 of the drug.

392
393 Identifying a more responsive population does not necessarily imply that there is no benefit in the
394 remaining population. It is therefore generally desirable to have some data in the non-selected (non-
395 enrichment) population to determine whether they respond less well, or indeed do not respond at all.
396 These data also can provide an assessment of safety in the non-selected population in the event that
397 such patients are exposed postapproval. The data need not be obtained in the controlled trials
398 supporting effectiveness but could be obtained in earlier studies. A qualitative estimate of
399 effectiveness might also be based on pharmacologic or even pre-clinical data. A strong mechanistic
400 rationale can make study of the non-enriched population unnecessary (e.g., study of effects in an
401 infection caused by a resistant organism).

402
403 A trial intended to provide evidence of effectiveness to support approval could include a broad range
404 of patients, but be prospectively designed to have as its primary endpoint the effect in the enriched
405 population subset. This is a standard (and unavoidable) approach when the baseline characteristic can
406 only be determined after randomization (e.g., the infectious organism or tumor characteristic), but the
407 approach (preferably with stratified randomization) is also valuable in other settings to gather some
408 information on the marker-negative population.

409
410 The following discussion considers predictive enrichment strategies in 5 categories:

- 411
- 412 • empiric strategies
 - 413 • pathophysiologic strategies
 - 414 • genomic strategies
 - 415 • randomized withdrawal studies
 - 416 • studies in non-responders or patients intolerant to other therapy
- 417
418

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419 **A. Empiric Strategies**

420
421 With an empiric strategy, the selection of likely responders for a study is not based on any
422 understanding of the basis for differences in response between patients, but on observations of a
423 response during screening periods, or prior experience with the drug or related drugs.

424
425 *1. Open Trial Followed by Randomization*

426
427 A straightforward enrichment strategy, in cases when a treatment response can be identified shortly
428 after treatment initiation, is to give open-label drug to all patients, identify apparent responders, either
429 on the planned study endpoint or on a biomarker or other short-term response thought to be predictive
430 of clinical response; withdraw the treatment; and then randomize only responders into a placebo-
431 controlled trial. This strategy is particularly useful when there is a low response rate. This strategy
432 has been discussed in the past²² and was used throughout the 1970s²³ to develop new anti-arrhythmic
433 drugs. Patients were titrated on the investigational agent until they had an acceptable reduction of
434 ventricular premature beats (VPBs). Only the responding patients were then randomized into placebo-
435 controlled trials, often fixed-dose, dose-response studies.

436
437 In the mid-1980s, controlled studies to evaluate topical organic nitrate patches randomized only people
438 who were shown immediately before the study to have an exercise angina response, or a blood
439 pressure response, to sublingual nitroglycerin. See also section 2 below (History of Response to a
440 Treatment Class).

441
442 The Cardiac Arrhythmia Suppression Trial (CAST) – a study of the mortality effect of suppressing
443 VPBs in patients with a recent acute myocardial infarction (AMI) and at least 6 VPBs per hour – is
444 one of the best known studies conducted in apparent responders.²⁴ It was known that people with > 10
445 VPBs per hour after an AMI had a 4-fold increase in the rate of sudden death. Previous failed
446 attempts to show survival benefits with antiarrhythmics had been criticized for the low rate of VPB
447 suppression achieved because many included patients did not respond. The CAST used an open-label
448 screening period to identify responders to two drugs, encainide and flecainide, shown to be very
449 effective in suppressing VPBs in a previous study.²⁵ Only patients who had at least a 70% VPB
450 reduction were randomized. Unfortunately, despite the enrichment effort, these anti-arrhythmic agents
451 did not decrease mortality but instead more than doubled it. This result reflects the inadequacy of the
452 surrogate endpoint of VPB reduction as a predictor of an effect on mortality, not the study design. The
453 enrichment design did, however, yield a study capable of showing an effect of VPB suppression and
454 allowed clear interpretation of the study, which showed, contrary to expectations, that even in VPB
455 responders, the drugs were not helpful and, indeed, were harmful.

456
457 *Note:* Use of an initial open-label phase without a control group does raise some concerns that need to
458 be considered when such a design is used. For example, in the CAST study there were deaths during
459 the screening period (not surprising given the recent infarction) that were difficult to interpret in an
460 open, uncontrolled setting where all patients received active drug. In CAST II²⁶ (ethmosin vs.
461 placebo), the initial screen for VPB suppression used a randomized comparison of drug to placebo,
462 with the responders then randomized into the placebo-controlled trial. This strategy showed that the
463 drug used in the screen was itself lethal (19 deaths on ethmosin vs. one on placebo) and the study was
464 stopped early.

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465
466 A similar problem was described in outcome trials of carvedilol in the treatment of chronic CHF.²⁷
467 These studies, unlike CAST, clearly showed a benefit of treatment. In two large studies, some patients
468 were excluded during a run-in period because they could not tolerate carvedilol. Some of those
469 patients died. The drop-out rates during the subsequent controlled trials were undoubtedly decreased
470 by the screening procedure that excluded patients intolerant to beta-blockers, and the results made
471 carvedilol seem better tolerated than it would actually be in patients starting therapy. The randomized
472 comparisons and the benefits demonstrated are fully valid in these trials for the populations studied,
473 but the benefits and risks facing unselected patients, who would be treated in clinical use of the drug,
474 may be different from those observed in the clinical trial, requiring close attention to the screening
475 period results.

476
477 There are many other outcome study settings in which it would be possible to select people more
478 likely to benefit from treatment. Patients with a lipid abnormality might be given the planned
479 treatment in a screening period to evaluate their biochemical response. For the randomized trial, only
480 people with a response of a certain size might be randomized, giving a greater mean effect on the lipid
481 level and, presumably, a larger effect on outcome. That approach could be useful in an early outcome
482 trial, but it would also be possible to randomize a broader population stratified by such an initial
483 response with the intent of making the primary study endpoint the result in the high-response subgroup
484 while gaining some information about the less responsive group. Again, the response in such a
485 selected group would not describe the response in an unselected population, an important issue for
486 labeling.

487
488 Active, open screening for empiric responders is particularly advantageous when a population is made
489 up of subsets (not identifiable pathophysiologically or genetically prior to treatment) with potentially
490 very different responses to interventions. It is hard to know in advance when this is true, but certain
491 difficult-to-study conditions, such as irritable bowel syndrome or fibromyalgia, might be candidates
492 for this approach.²²

493
494 The overall strategy (open trial followed by randomization) is a very efficient way to document
495 effectiveness, but it cannot be used prospectively to identify the responder population when the drug is
496 used in clinical practice. In some cases, however, an early response could be used to determine who
497 should stay on the drug, essentially how all symptomatic treatments are used.

498
499 *2. An Individual's History of Response to a Treatment Class*

500
501 Information about prior response to a drug in a pharmacologic class, if available, can be used to
502 identify potential responders for a study of a new member of that class. As is the case with an open
503 label trial followed by randomization, use of patient history of response to a drug class can greatly
504 increase the efficiency of a trial in demonstrating effectiveness. In most cases, however, it will not
505 help identify the population to be treated in clinical practice.

506
507 A study enriched with prior responders to a pharmacologic class can be useful in demonstrating
508 effectiveness at the proof-of-concept stage. This design may be particularly advantageous for
509 randomized, fixed-dose, dose-response studies (the preferred dose-response study design described in
510 the ICH guidance *E4, Dose-Response Information to Support Drug Registration*²⁸). A responder

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511 population provides a larger overall treatment effect and, therefore, a steeper dose-response curve,
512 which generally allows for easier interpretation of the curve (identifying the steep area and plateau of
513 the curve) and more precise characterization of dose-response, especially for doses providing near-
514 maximum effects. For example, a dose-response study of indapamide in known responders to
515 diuretics demonstrated mean decreases of 29/12 mmHg (systolic/diastolic) for the 2.5 mg dose and
516 37/15 for the 5 mg dose, an increase in effect with the 5 mg dose considerably larger than that seen in
517 studies of unselected patients, where 2.5 mg and 5 mg gave similar results.

518
519 **3. *Factors Identified in Results from Previous Studies***
520

521 Analyses of results of previous trials can sometimes point to a substantially greater effect in a
522 specific subset of the overall population and provide a basis for studying that subset in a
523 subsequent study, either as the sole population studied or as the identified primary endpoint subset
524 in a study of a broader population. For example, BiDil, a treatment for severe CHF, was
525 approved²⁹ on the basis of a placebo-controlled study carried out entirely in self-identified blacks
526 (the African-American Heart Failure Trial (A-HeFT)).³⁰ The selection of a black population was
527 based on two previous studies (the Vasodilator-Heart Failure Trials (V-HeFT) I and II^{31,32}) of a
528 hydralazine hydrochloride – isosorbide dinitrate combination vs. placebo in a racially mixed
529 population that strongly suggested effectiveness in blacks. In those studies, the combination had
530 not shown an overall benefit, but post-hoc analyses revealed a nominally significant effect in black
531 patients in V-HeFT I and apparent equivalence to enalapril in V-HeFT II. In contrast, there was
532 little or no effect of the combination in whites in V-HeFT I and nominally significant inferiority of
533 the combination to enalapril in whites in V-HeFT II. The replication of the observed effect in
534 blacks was strong, with only a suggestion of a modest effect in whites, perhaps a third of the effect
535 in blacks. A trial to establish this small effect in a white population would have required 16,000
536 patients. The product was approved for “self-identified blacks” only.

537
538 **B. *Pathophysiological Strategies***
539

540 These strategies involve selection of likely responders based on the patient’s individual physiology or
541 on assessment of disease pathophysiology that suggests that only certain patient subgroups will
542 respond to a particular therapy or that certain subgroups will respond better than others.

543
544 **1. *Metabolism of the Test Drug***
545

546 For a drug that acts through an active metabolite, as is the case for the antiplatelet drug clopidogrel,
547 patients may differ in their ability to metabolize the prodrug to its active metabolite. Some patients
548 may not form the active metabolite at all and others may not make enough to respond to the dose
549 selected. Including these patients in a trial will dilute the overall drug effect and can also lead to
550 inefficient or inappropriate use of the drug in practice if the two subsets of patients are not identified
551 and treated differently. In some cases, it will be possible to adjust (increase) the dose in the poor
552 metabolizers, but patients who cannot make the active metabolite at all should probably be excluded
553 from the trial or from the planned primary analysis. A closely related approach is the assessment of
554 uptake of the test drug by a tumor.³³ Historically, before treatment of thyroid tumors with I-131, a low
555 dose was given to determine whether the tumor did, in fact, take up iodine and to what extent, so that
556 the needed dose could be estimated.

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2. *Effect on Tumor Metabolism*

It may be possible to select patients for a cancer trial by screening for an effect on a tumor metabolic response, as assessed by a positron emission tomography (PET) scan. For example, response to the tyrosine kinase inhibitors imatinib and sunitinib in patients with gastrointestinal stromal tumors (GIST) has been shown to correlate well with metabolic responses (decreased tumor glucose utilization) assessed by 15F-fluorodeoxyglucose (FDG) PET imaging.³⁴ The clinical trial could enter only the identified metabolic responders or enter all patients, stratified by metabolic response. In the second case, the primary hypothesis could be the treatment effect in the metabolic responder stratum.

3. *Proteomic Markers and Genetic Markers Linked to a Proteomic Marker*

Increasingly, cancer treatments are directed at enzymatic, hormonal, or other functions that are tied to tumor surface intracellular receptors. The following examples illustrate use of proteomic markers, or genetic markers that are linked to a proteomic marker, that are known to be essential for the activity of the drug.

- Trastuzumab was developed to bind to the Her-2-neu receptor, which is present on normal and malignant cells but is over-expressed in about 25% of breast cancers. Binding of trastuzumab to the Her-2 neu receptor blocks receptor-mediated growth-stimulating intracellular signaling, decreasing cellular repair after chemotherapy and radiation therapy and also increasing apoptosis. In activity-estimating trials, anti-tumor activity in patients with lower levels of Her-2-neu receptor expression (1+ by immunohistochemical staining) was minimal, so that definitive efficacy trials in patients with metastatic disease were limited to patients with Her-2-neu 2+ or 3+ over-expression. In the treatment of metastatic disease, when added to either of two background regimens, trastuzumab increased survival by a mean of about 5 months, about 3 to 4 times the effect that would have been expected in an unselected population, assuming no response (which a modest amount of testing showed was the case) in the Her-2-neu negative patients. Enrichment thus allowed a modest-sized study to show a striking effect and directed treatment to the population that could benefit. In addition, because the drug was shown to be moderately cardiotoxic in the metastatic breast cancer trials, in designing adjuvant studies it was considered critical to focus on potential responders (i.e., patients with Her-2-neu receptor over-expression).³⁶
- Imatinib was developed to treat patients with gastrointestinal stromal tumor (GIST), a tumor not previously responsive to antineoplastic therapy. Imatinib inhibits c-Kit, a receptor tyrosine kinase that is mutated and activated in a large majority of GIST patients, resulting in abnormal proliferation of tumor cells. In a small study (N=147) in patients with a pathologic diagnosis of c-Kit-positive unresectable and/or metastatic malignant GIST, 56 patients responded and 55 of the responding patients demonstrated a durable partial response of 7-38 weeks (median 13 weeks). This study was followed by a placebo-controlled, adjuvant therapy trial using imatinib in GIST patients with c-Kit expression in whom complete gross resection of GIST had been performed. The study showed a substantial increase in recurrence-free survival at a median follow up of 14 months.³⁷

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- 603 • Evidence from the metastatic breast cancer setting has demonstrated that the likelihood of
604 response to endocrine therapy is related to the hormone receptor status of the tumor. For
605 example, when treated with tamoxifen, a selective estrogen receptor modulator, patients
606 whose tumors express both estrogen receptors (ER) and progesterone receptors (PR) have a
607 response rate of approximately 70%; patients whose tumors express either ER or PR, but
608 not both, had a 40% response rate; and patients whose tumors are ER and PR negative have
609 a response rate less than 5%. As a consequence, testing of all breast cancer specimens to
610 direct decisions regarding endocrine therapy, in both the early-stage and the advanced
611 setting, has become the standard of care³⁸ and would be expected in any trials of endocrine
612 therapy.
613
- 614 • A more recent illustration is the use of somatic mutations in the gene encoding the serine-
615 threonine protein kinase BRAF to identify potential responders to vemurafenib in
616 melanoma; 40% to 60% of all melanomas carry this activating mutation. In an initial study
617 in 49 patients with melanoma, 11 of 16 patients with BRAF^{V600E} who received vemurafenib
618 had a tumor response, compared to 0 of 5 without the mutation (the remaining 28 patients
619 did not undergo BRAF mutation testing). The phase 3 trial in 675 patients with metastatic
620 or unresectable melanoma who had the BRAF^{V600E} mutation compared vemurafenib to
621 dacarbazine. The trial was stopped after an interim analysis showed a 63% reduction in the
622 risk of death with vemurafenib. The confirmed response rate was 48% for vemurafenib
623 versus 5% for dacarbazine.³⁹
624

625 The examples of pathophysiologic selection just described reflected, at least initially, tumor receptor
626 variables that could be described as proteomic variables, but that were in many cases later identified as
627 tumor genetic markers (EGFR and BRAF genetics, for example). In such cases the genetic marker
628 defines a pathophysiologic effect.
629

630 When proteomic and genetic markers are used in an enrichment strategy, adequate characterization of
631 the test for the marker is critical. An inaccurate assay will undermine an enrichment effort if the study
632 aims to demonstrate superiority or non-inferiority of the test treatment.⁴⁰ It is also important to gain as
633 much information as possible about the marker-response relationship (sensitivity and specificity).
634

635 **C. Genomic Strategies**
636

637 To date, most genomic enrichment strategies have involved tumor genomics. Although most genomic
638 markers (e.g., for a tumor surface property) have been linked to a pathophysiologic property, this
639 linkage is not essential. Use of a genomic marker could instead be an empiric strategy, identifying
640 responders without providing a pathophysiologic basis for the difference in response.
641

642 Any genetic differences that predict response must in the end have some pathophysiologic basis, but
643 enrichment strategies to identify responsive patients could be used before recognition of a mechanism.
644 Studies directed at tumors with specific genomic patterns that appear to predict outcome (e.g., tumors
645 with mutations in a target gene, genome-wide expression profiles, SNP arrays) are becoming
646 increasingly common. One difficulty is that relationships between genetic patterns and outcomes are
647 often found only after study results are known. Markers discovered this way will have credibility
648 problems related to the post-facto nature of the finding and will almost always need confirmation in a

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649 prospectively planned enriched study. Such findings are of particular concern when overall study
650 results show no effect. As a general matter, preservation of study specimens and analysis of results by
651 various genomic markers are increasingly prevalent practices and are of great potential value, whether
652 they lead to an enriched study following a failed trial, or to better targeted therapy after a successful
653 trial.

654
655 Freidlin and Simon,⁴¹ however, have proposed a novel, prospective approach that makes use of
656 genomic data collected on all randomized subjects during the conduct of a study:

- 657
658 1. Design the study as usual, but divide it into first and second halves. Prospectively allocate the
659 overall study alpha as 0.04 for the whole population and 0.01 for a patient subset to be
660 identified in the first half of the study.
- 661
662 2. Run the first half of the study and conduct unblinded data analyses, searching for a genetic
663 predictor of response. There would be no limit to the number of such analyses conducted. A
664 single genetic subset appearing to predict response may be identified.
- 665
666 3. Complete the remainder of the study, entering patients according to the original eligibility
667 criteria (both the predicted responders and predicted non-responders) as before.
- 668
669 4. At the conclusion of the study, the effect in the entire study population is tested at an alpha of
670 0.04, and the genetically identified subset is tested only in the second half at an alpha of 0.01.
- 671
672 5. The study shows evidence of effectiveness if either analysis is positive. When the responder
673 population is a small fraction of the total population, but exhibits a large response, this design
674 can improve the chance of detecting a treatment effect. It also retains good power for the
675 overall study if the drug is more broadly effective.

676 A similar approach that avoids delay while the genomic marker is being evaluated might also be
677 considered⁴²:

- 678
679 1. Run the planned study, again prospectively dividing the available alpha between the overall
680 study population and a subset to be identified later.
- 681
682 2. Whether the overall population analysis is positive or negative, take a random sample of the
683 study population (50%, 33% or another fraction) and search for a subset with a genomic
684 pattern (or, for that matter, any other subset) showing a substantial differential effect. This first
685 analysis would be considered wholly exploratory. It would be important to have genomic
686 assessments on a substantial portion of all subjects.⁴³
- 687
688 3. Examine the remaining data, considering only the genomic subset found positive in the first
689 sample. As long as the second part was kept blind until after the first analysis and only the
690 marker-positive subset is tested, study-wide alpha error will be preserved. Any such approach
691 would need scrupulous attention to maintaining the blind, perhaps by using an independent
692 group to do the genomic search.

693 For anti-viral drugs it can be anticipated that there will be cases in which either host or viral genomics
694 plays a role in determining drug response. For example, genome-wide association studies have
695 identified host IL28B gene variants associated with the likelihood of a viral response to

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693 ribavirin/interferon regimens to treat Hepatitis C virus (HCV). This association has been
694 independently substantiated in multiple studies and can distinguish patients with a low (about 25%) or
695 high (about 80%) likelihood of sustained viral response,⁴⁶ to a pegylated interferon plus ribavirin.

696
697 It is also well documented that HCV viral genotype determines the needed duration of therapy and
698 predicts likelihood of response. Six genotypes have been identified. Genotype 1 is the most prevalent
699 genotype in the United States and is more resistant to treatment than genotypes 2 and 3. Patients with
700 genotype 1 treated with a pegylated interferon and ribavirin for 48 weeks had a sustained virologic
701 response of 40 to 50%. Patients with genotypes 2 and 3 had sustained responses of 80% or more with
702 only 24 weeks of treatment with pegylated interferon and ribavirin.⁵⁷ Two protease inhibitors, direct-
703 acting antiviral agents boceprevir and telaprevir, have been shown to provide greatly improved
704 sustained viral response and the potential for reduced duration of total treatment in patients with
705 genotype 1 virus, when added to ribavirin/interferon.

706
707 **D. Randomized Withdrawal Studies**

708
709 In a randomized withdrawal study, patients who have an apparent response to treatment in an open-
710 label period or in the treatment arm of a randomized trial are randomized to continued drug treatment
711 or placebo. As such trials generally involve only patients who appear to have responded, this is a
712 study enriched with apparent responders, an empiric strategy. The study evaluation can be based on
713 signs or symptoms during a specified interval (e.g., blood pressure or angina rate), on recurrence of a
714 condition that had been absent (e.g., depression), or on the fraction of patients developing a rate or
715 severity of symptoms that exceeds some specified limit (a failure criterion).

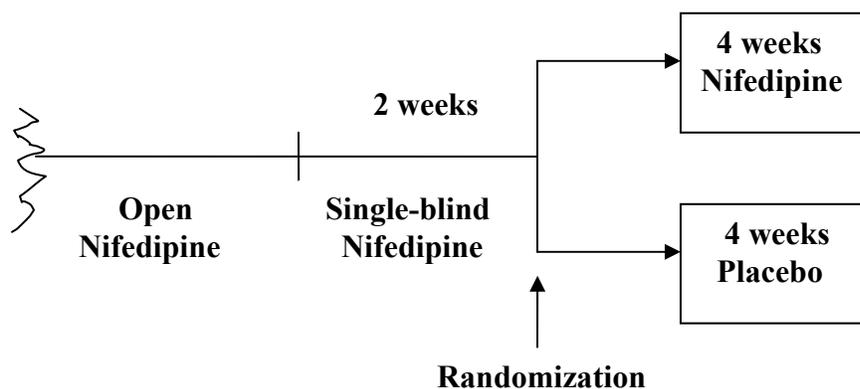
716
717 The randomized withdrawal design was proposed as a way to establish long-term effectiveness of
718 drugs in settings in which long-term use of a placebo would not be acceptable (e.g., most psychiatric
719 and antihypertensive drug treatments).⁴⁶ Even in settings in which long-term placebo use may be
720 acceptable, however, it is generally difficult to recruit patients, and drop-out rates are often high,
721 posing difficult analytic problems. A randomized withdrawal design in which the study population is
722 on treatment for an extended duration followed by blinded, randomized withdrawal of treatment for a
723 short duration could provide evidence of prolonged effectiveness with only brief exposure to placebo.
724 The design allows a patient to be removed from the study (for having reached an endpoint) when the
725 condition returns at specified severity, avoiding long-term exposure to an ineffective treatment.⁴⁸

726
727 The randomized withdrawal design can also be used as an initial trial to show effectiveness when there
728 is an existing population of patients in an open-label treatment setting (e.g., under an IND or as an off-
729 label use of an approved drug), as illustrated by the cases of nifedipine and gamma-hydroxybutyrate.

730
731 The approval of nifedipine for vasospastic angina (the first drug approved for this condition) illustrates
732 the utility of this design. An open-label, historically controlled trial⁴⁷ was considered inadequate to
733 support approval because the natural history of vasospastic angina was not well-established. A
734 randomized withdrawal design (see Figure 2) was conducted in patients already receiving the drug,
735 with a primary endpoint of recurrence of severe vasospastic angina leading to study withdrawal. A
736 total of 28 patients participated in the study. One-third of the patients randomized to placebo
737 withdrew early, as compared to no withdrawals in patients randomized to nifedipine (see Table 2).

738

739 **Figure 2: Nifedipine Randomized Withdrawal Trial in Vasospastic Angina**



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743

Table 2: Results of Nifedipine Randomized Withdrawal Study

	Nifedipine	Placebo
N	13	15
Early withdrawal	0	5*
Early withdrawal or AMI	0	6*

* Statistically significant at $p \leq 0.05$

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Another example in which patients already using a drug were studied was gamma-hydroxybutyrate (GBH, sodium oxybate), which was approved for treatment of cataplexy on the basis of a single placebo-controlled study of conventional design and a second, small, randomized withdrawal study in 55 long-term (7 to 44 months) users randomized to 2 weeks of continued treatment with GBH or placebo. The second study produced a clinically and statistically impressive result, as shown in Table 3, and needed little time for recruitment.

Table 3: Randomized Withdrawal Study of GHB in Cataplexy

Treatment Group	Median Attacks/2 weeks	
	Baseline	Change in Rate
Placebo (n=29)	4.0	+21.0
GHB (n=26)	1.9	0
P < 0.001		

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By randomizing patients to different doses, the randomized withdrawal design can also be used to obtain long-term dose-response data. For example, this design was used to demonstrate effectiveness of a single weekly dose of fluoxetine in preventing recurrence of depression; patients on 20 mg/day were randomized to placebo, fluoxetine 70 mg/week as a single dose, or continued 20 mg per day. Both fluoxetine groups were superior to placebo in reducing the rate of recurrence.

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764
765 A randomized withdrawal design may also be useful in establishing the duration of benefit of long-
766 term treatments, an issue of great interest for drugs with long-term toxicity concerns and a potential for
767 long, post-treatment benefit. For example, the original node negative adjuvant tamoxifen breast
768 cancer trial (NSABP B-14)⁴⁸ randomized 2,892 women with node-negative, hormone receptor-positive
769 breast cancer to receive 5 years of tamoxifen versus placebo. Tamoxifen reduced the risk of
770 recurrence by 41% and the risk of death by 33% and was rapidly adopted as the standard of care. A
771 second randomization was then performed in which the 1,166 patients who had received tamoxifen
772 were assigned to receive either an additional 5 years of tamoxifen or placebo. The trial was halted by
773 the data monitoring committee after an interim analysis revealed that continuing the study could not
774 demonstrate an advantage for continued tamoxifen use and suggested that tamoxifen was harmful.
775 There was a non-statistically significant trend in both disease free survival (DFS) and overall survival
776 (OS) favoring the placebo group and an increase in new malignancies in the tamoxifen group. Similar
777 designs have been used to examine long-term effects of bisphosphonates.

778
779 **E. Studies in Non-responders or Patients Intolerant to Other Therapy**
780

781 A study can be enriched by selection of patients who failed to respond to an existing drug, or who
782 were intolerant of that drug. Although non-responders or treatment intolerants are not more likely
783 than an unselected population to respond to or tolerate the new drug, they would generally be less
784 likely to respond to or tolerate the existing drug, giving the test drug an enrichment advantage.
785 Because patients in a trial sometimes respond to a drug to which they had previously failed to respond,
786 in most cases studies in non-responders are informative for the between-drug comparison of
787 effectiveness only if patients are randomized to both the new and failed drug (i.e., not simply placed
788 onto the new drug in a single arm study or randomized to new drug versus placebo). This approach
789 can also provide important information to practitioners; it is critical to know whether another member
790 of a pharmacologic class or a member of a different class can be useful in patients who fail on a
791 previous treatment. The approach may be useful in two settings:

- 792
- 793 • To demonstrate the effect in non-responders to previous therapy of a drug that may not be
794 more effective overall than existing therapy in an unselected population, but that has a different
795 responder population. A drug that acts through a mechanism different from that of existing
796 treatments might be effective in non-responders to the existing drug.
797
 - 798 • To efficiently demonstrate the treatment effect of a new drug that is actually moderately
799 superior to the existing drug, but where a very large study would be needed to show superiority
800 if the study included unselected patients, many of whom would respond to the less effective
801 drug. For example, if the new drug response rate is 90% and the existing drug response rate is
802 80%, a study with 90% power to detect that 10% difference would require about 600 patients.
803 In contrast, if only non-responders to the existing drug were randomized (20% of the patients
804 treated with the existing drug), few would respond to the existing drug, and at least half of the
805 patients would respond to the new drug, a difference detectable with fewer than 40 of the non-
806 responders.
807

808 *Note:* In neither case would showing an advantage for the new drug in non-responders to previous
809 therapy establish overall superiority of the new drug.

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I. Studies in Non-Responders

a. Captopril

To support a claim in severe hypertension unresponsive to other agents, a study was designed to evaluate patients who had not responded to standard triple therapy (propranolol 320 mg, hydrochlorothiazide 100 mg, and hydralazine 200 mg) (there were many escape pathways for non-responding patients so that they would not be untreated). Patients who had failed triple therapy and had diastolic pressure that was severely elevated were observed for 1 to 2 weeks on the same regimen (triple therapy lead-in) and, if their diastolic pressure did not exceed a defined limit, randomized to the same standard triple therapy they had failed on, or to captopril, with a 2:1 captopril to triple therapy randomization ratio. The number of responders (diastolic pressure less than 90 mmHg or fall of at least 10 mmHg, but not to below 90 mmHg diastolic) clearly favored captopril in this difficult-to-treat population (Table 4).

Table 4: Results of the Captopril Severe Hypertension Trial for the Group Randomized to Captopril or Triple Therapy

		Captopril	Triple Therapy
	Total number analyzed	66	30
Week 4	Normalized DBP \leq 90	21 (33%)	5 (17%)
	Reduction in DBP \geq 10	8 (13%)	3 (10%)
Week 8	Normalized (DBP \leq 90 mmHg)	22 (34%)	4 (14%)
	Reduction in DBP $>$ 10 mmHg	14 (22%)	3 (10%)

Note: approximately 25% of the triple therapy *non-responders* did respond to the previously failed therapy in the new trial. This finding reinforces the need for randomization to the new and reportedly failed therapy in a study in non-responders. A study that had merely switched patients from the failed therapy to the new one and found 25% responders might have been interpreted as showing an effect of the new drug in the non-responders to prior therapy when, in fact, it would not have demonstrated that.

b. Clozapine

Clozapine is an antipsychotic agent associated with serious toxicity, a greater than 1% rate of potentially fatal agranulocytosis. For clozapine to be approved, it was crucial to show that it offered a clear advantage over safer alternatives. To show this, a study was conducted in hospitalized schizophrenic patients with a history of poor response to neuroleptics who, in addition, had failed to respond to 6 weeks of treatment with haloperidol. These patients were randomized to 4 weeks of treatment with clozapine or chlorpromazine plus benztropine. The results showed a striking advantage for clozapine on Clinical Global Impression (CGI) and British Psychological Rating Scale (BPRS) standard measures in antipsychotic drug trials (see Table 5). Despite its serious risk, clozapine was approved for use in patients not responding to other anti-psychotic agents.

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Table 5: Results of Clozapine Study in Non-responders to Standard Psychotropic Agents

Measure	Response (%)	
	Clozapine	Chlorpromazine
CGI (decrease > 1)	71	37
BPRS Items (decrease > 1)		
Concept disorganization	60	39*
Suspiciousness	64	42*
Hallucinations	59	51
Thought content	15	2*
CGI and BPRS	15	2*

* p < 0.05

CGI = Clinical Global Impression

BPRS = British Psychological Rating Scale

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c. Rofecoxib

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It is widely believed that individual patients respond differently to different NSAIDs. To examine this belief, a controlled trial was conducted in which osteoarthritis patients identified as non-responders to celecoxib were randomized to celecoxib or rofecoxib. In fact, there was no observed difference (Figure 3).

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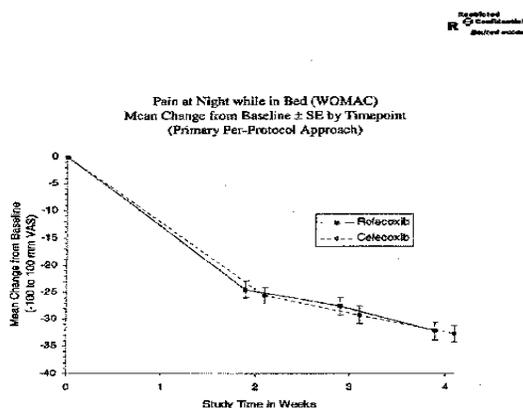
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Figure 3: Study Comparing Rofecoxib to Celecoxib in Celecoxib Non-Responders



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Note: there was considerable and prompt improvement in pain in both groups. A baseline-controlled, single-arm trial of rofecoxib would have led to a clearly erroneous conclusion, and even a placebo-controlled trial of rofecoxib in this population might have shown an effect that would have been incorrectly interpreted as an effect in celecoxib non-responders.

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2. *Study in Intolerants: Angiotensin Receptor Blockers (ARBs) in People Who Cough on Lisinopril*

Studies of the tolerability of a new drug in people who do not tolerate a previous treatment are also informative and efficient. Comparative studies in an unselected population could provide some information on relative tolerability, but a very large study would be needed to show small differences. For example, if the true rates of cough for an angiotensin converting enzyme inhibitor (ACEI) and an angiotensin II receptor antagonist (ARB) were 5% and 1%, respectively, a study with 90% power to show a difference in an unselected population would need about 800 patients. In contrast, a study in patients known to cough on ACEIs would need fewer than 20 patients, if, for example, the cough rate were > 90% in the ACEI arm and 20% in the ARB arm.

This approach was used in a study of 84 elderly hypertensive patients with a history of coughing on an ACEI.⁴⁹ They were then withdrawn from their ACEI and given 8 weeks of the ACEI lisinopril, which had to cause at least moderate coughing for patients to continue on the study. Lisinopril was then withdrawn for 4 weeks and coughing had to disappear. The patients were then randomized to losartan 50 mg, lisinopril 10 mg, or metolazone (diuretic active control that does not induce coughing) for 10 weeks. The study achieved a very persuasive result with this small population (see Table 6).

Table 6: Comparison of Coughing Rates with ARB, ACEI, and an Additional Active (Non-Cough-Inducing) Control

	Lisinopril	Losartan	Metolazone
	N = 28	N = 28	N = 28
Any Cough	97%	18%	21%
	P < 0.001		

VI. ENRICHMENT STUDY DESIGN AND OTHER CONSIDERATIONS

A. General Considerations

In general, enrichment studies should incorporate the established principles of well-controlled studies, controlling bias (randomization and blinding), and studywise type I error (see section VI.C).

An enrichment design should be explicitly described in the protocol and study report and should fully detail the enrichment maneuvers and their impact on interpretation of results. For example, if only half of patients screened meet the selection criterion, the implications of this finding on expected response rate in the overall population and generalizability of the results should be evaluated. Such descriptions are particularly important for trials in which high-risk patients (prognostic enrichment) and probable responders (predictive enrichment) have been selected, when the description is critical to knowing to which patients the results apply.

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912 1. *Performance Characteristics of a Screening Strategy for Selecting Patients*
913

914 Some prognostic and predictive enrichment strategies depend heavily on a screening measurement for
915 selecting the enriched population. For less well-established measures, such as use of proteomic and
916 genomic markers to identify responder populations, there are generally more performance
917 uncertainties than for phenotypically well-known prognostic factors such as blood pressure or
918 cholesterol. It is critical to understand, to the extent possible, the accuracy of the test used for
919 enrichment, as well as the performance characteristics (sensitivity, specificity) of the measurement
920 used. If a selection criterion does not accurately distinguish patients, the effect of enrichment is
921 weakened. If a classifier is overly inclusive (lacks specificity), the estimated difference between the
922 effect in the enriched and non-enriched populations will be attenuated, defeating the goal of the
923 enrichment strategy. If a classifier is overly exclusive (i.e., lacks sensitivity), patients who could
924 benefit from the drug will not be studied, and study subjects will be needlessly difficult to find. In a
925 non-inferiority study, an inaccurate classifier would bias the study toward a finding of no difference.⁴⁰
926

927 Apart from the adverse impact of a poor classifier on a study, the performance characteristics of the
928 classifier remain important if the classifier is to be used in selection of patients after approval of the
929 drug. In some cases, the performance characteristics of a classifier will be well-documented in earlier
930 studies, but the enriched trial may itself constitute an important source of information about the
931 sensitivity and specificity of the classifier. For example, by including patients above and below a
932 presumed classifier cut off and examining results by classifier status, it is possible to assess the
933 quantitative relation of the enrichment factor to response (e.g., the relationship of a receptor level such
934 as HER 2/neu to response). This relationship can be explored even if the primary analysis defines the
935 marker-positive population of interest on the basis of a pre-specified cut-off. The classifier is pertinent
936 not only to selection of patients for the study, but to selection of patients for treatment once the drug is
937 marketed. Planned interim evaluations could be used to narrow selection criteria, especially if there
938 were a measure of effect that could be assessed early (e.g., short-term pharmacologic effect).
939

940 2. *When Should a Classifier Be Developed and Characterized?*
941

942 During a development program using an enrichment strategy, it is not always clear when the
943 performance of a classifier should be characterized, nor how well the classifier and assay
944 methodologies must perform if they do in fact define a population with increased response. Answers
945 to these questions depend in part on when during development it becomes clear that an enrichment
946 strategy should be used and how critical enrichment will be to successful drug development and
947 approval. When there is not strong pre-existing information defining a responder subset, early
948 exploratory studies that include patients over a broad range of values of the enrichment factor can be
949 used to develop criteria for classifying patients for subsequent enrichment studies. If the need for
950 classifier-based patient selection does not become apparent until late in development, it is also possible
951 to first characterize a classifier in a phase 3 trial. When the classifier is not based on an intrinsically
952 binary measurement, the trial could explore a range of threshold values for a classifier that would be
953 used to identify patients for the primary analysis, but this must be planned in advance to control the
954 Type I error rate of the study. With few exceptions, the enrichment characteristics used in
955 confirmatory studies should be measured at baseline, and patients who are classified as having, or not
956 having, the predictive marker should be stratified and randomly assigned to treatments if both
957 subgroups of patients are to be included. If the classifier is known only after randomization, but is a

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958 baseline characteristic, randomization should be effective even without stratification, as long as the
959 sample sizes in the treatment groups within each marker-defined subgroup are large enough to balance
960 important prognostic baseline factors.⁴³

961
962 **B. Which Populations to Study**

963
964 As will be described in more detail below, trials can be designed (1) to include only patients with the
965 enrichment factor or (2) to include patients with and without the enrichment factor, but with an intent
966 to analyze only the patients with the enrichment factor as one of the primary study hypotheses.
967 Studies including both populations need not include a wholly unselected population of patients with
968 the disease to be treated, but can designate separate sample sizes for patients with and without the
969 enrichment characteristic to collect sufficient information to demonstrate effectiveness in the enriched
970 subgroup and also to allow a reasonable estimate of effect in the non-enriched group. Many design
971 alternatives have been discussed in the literature.^{50,51}

972
973 A critical question in all settings in which enrichment is used is therefore the extent to which the
974 enrichment marker-negative population should be studied, an issue that may bear importantly on how
975 a drug would be labeled. In some cases, study of the general population (one including the marker-
976 negative population) would not be expected. For example, if prognostic enrichment is used to ensure
977 that there are sufficient events to make a trial feasible, even if it is thought that the treatment effect
978 would also be present in the lower-risk population without the marker (but at a lower absolute effect
979 size), it may not be possible to design a trial that includes a significant fraction of the marker-negative
980 population without greatly increasing the sample size needed – a strategy that may make the trial
981 impractical and defeat a major purpose of prognostic enrichment. The Clinical Studies section of
982 labeling and sometimes the Indications section would identify the population studied and comment, as
983 appropriate, on use in other populations. Advice regarding use in the untested marker-negative
984 population would depend on the particular circumstances. For example, the presence of significant
985 toxicity could lead to doubts about the advisability of using the drug in the lower-risk population. The
986 heterogeneity-reducing factors discussed in Section III would not ordinarily call for study of the
987 population lacking the enrichment factor (e.g., poor compliers).

988
989 It is principally in the area of predictive enrichment, especially predictive enrichment using a
990 pathophysiological or genomic marker, that the question of studying the population without the
991 enrichment factor is most germane. Experience suggests that the selected enrichment factors often do
992 not prove to precisely dichotomize patients into subpopulations that will and will not respond, so that
993 it is usually desirable to obtain some information on the marker-negative population to assess
994 performance of the factor. However, even an imperfectly characterized predictive marker can greatly
995 increase the power and likelihood of success of a study. Moreover, in treating serious and life-
996 threatening illnesses, especially when there are alternative treatments, using the test treatment in
997 patients thought unlikely to respond raises critical ethical issues.

998
999 Efforts to use predictive enrichment thus offer a number of design choices. The study designs
1000 illustrated below are fixed sample size designs that can be used with predictive enrichment strategies
1001 (also see section VI.D below concerning adaptive enrichment and non-fixed sample size). The
1002 examples all describe trials intended to show superiority of the test treatment to a control (placebo,
1003 standard of care), but non-inferiority studies would present similar issues.

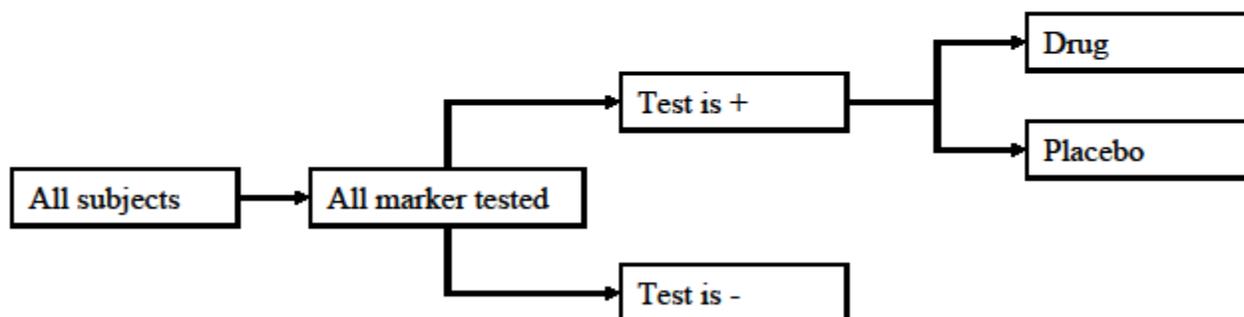
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1. *Studying Marker-Positive Patients Only*

A study randomizing only marker-positive patients is shown in Figure 4. Because a study that uses a marker-positive only population will provide no direct information about the marker-negative population, its use should generally be limited to situations in which information about the marker-negative population is not needed or is not feasible given the objectives of the study. For example, if it appears clear, based on mechanistic, pre-clinical, or early clinical data, that the marker-negative patients will have no or minimal response or would be exposed to unreasonable risk, inclusion of the marker-negative patients would, in most cases, not be justified.

Figure 4

Prospective, Screened - no possible effect in the marker-negative group



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The study shown in figure 4 would support an effectiveness claim for the enriched population, but it would overstate the actual effectiveness for an unselected population, so that the fraction of patients with the marker would be important information. The study would provide no new clinical evidence with respect to the marker negative population and would not further characterize the predictiveness of the marker because there would be no ability to compare effectiveness. Because there will be no effectiveness or safety information on the enrichment-marker-negative patients, it is implicit in this approach that the selection process would be fully described in the labeling and that in clinical practice, in most cases, all patients would be tested for the enrichment marker before exposure. Moreover, because assessment of marker status is critically important to effectiveness in patients in clinical practice, it would generally be expected that the enrichment marker would be measured after

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1031 approval using an established, FDA approved, laboratory test explicitly labeled for this purpose as a
1032 companion diagnostic.⁵⁵

1033
1034 2. *Studying Both Marker Positive and Negative Patients*

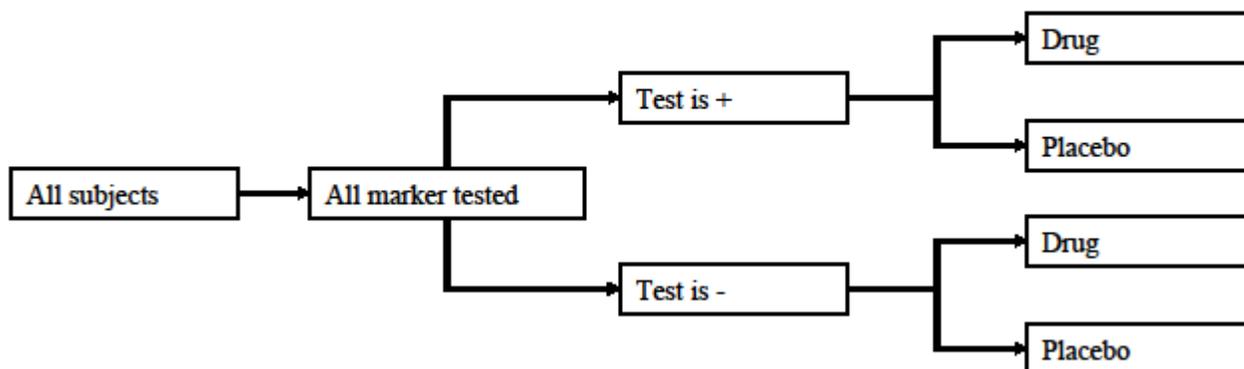
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1036 We encourage inclusion of some predictive marker-negative patients in most trials intended to provide
1037 primary effectiveness support, unless it has been well established in earlier studies that the marker-
1038 negative patients do not respond, or there is a strong mechanistic rationale that makes it clear that they
1039 will not respond. In general, the greater the uncertainty about the marker cut-off and responsiveness
1040 of marker-negative patients, the more important it is to include a reasonable sample of marker-
1041 negative patients. When substantial incentive exists to use the drug in the marker-negative population
1042 (e.g., for serious diseases with few alternative therapies), characterization of the response in the
1043 marker-negative population is more important, especially if the drug has important safety concerns.

1044
1045 There are two cases to consider in studies that include marker-positive and marker negative patients:
1046 (1) when the marker can be assessed before randomization and (2) when the marker can be assessed
1047 only after randomization. Figures 5A and 5B provide sample study designs for these two cases.⁵¹

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Figure 5A

Patients Prospectively Screened and Stratified - where there is possible effect in the marker-negative group

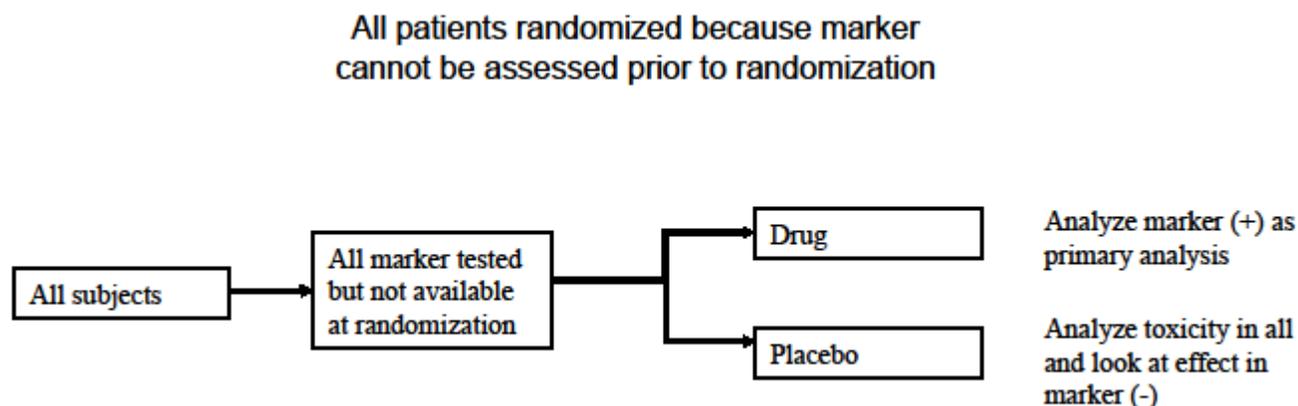


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1054 In the first case, marker status is determined for all patients, and randomization is stratified by marker
1055 status. The primary study objective would usually be a statistically rigorous demonstration of the
1056 treatment effect in the marker-positive patients, and the study would therefore be powered for the
1057 effect in that group. The size of the marker-negative group would be determined separately (i.e., it
1058 would not be necessary to randomize all marker-negative patients). Because the treatment effect
1059 would be expected to be much smaller (if there were any effect) in the marker-negative population, the
1060 size of the marker-negative population would usually be too small to give a definitive answer on the
1061 effect in that population; however, it would provide at least some estimate of the effect in that
1062 population. The design could also provide an overall risk–benefit assessment for the drug in a general
1063 population, which would be advantageous if some exposure in marker-negatives is anticipated in

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1064 clinical practice (e.g., because the test is not widely available). When there is substantial uncertainty
1065 about whether a marker is predictive, (i.e., can select a population in which treatment is effective), the
1066 primary endpoint could be the effect in the overall population, or study alpha could be divided
1067 between the two endpoints (overall population and marker-positive population).⁵²

Figure 5B



1072
1073
1074 The second case (Fig 5B) is one in which a drug that is expected to be effective only in the marker-
1075 positive subset (e.g., only in patients with a sensitive organism) must nonetheless be given to all
1076 patients because the marker result is not available at randomization. It would still be appropriate to
1077 have the primary study outcome be the effect in the marker-positive subset, but the risk-benefit
1078 assessment would reflect results in the entire population (i.e., the population that would be exposed to
1079 treatment). In these cases, when marker test results for patients using the drug will not be known
1080 before drug administration and if no patient management decisions will be made on the basis of the
1081 test result (e.g., decisions to discontinue treatment in marker-negative patients), FDA approval of the
1082 test prior to approval of the drug is not needed.

1083
1084 3. *Studies in Alternative Therapy Non-Responders to Support Claim of Effectiveness in*
1085 *Non-Responders*

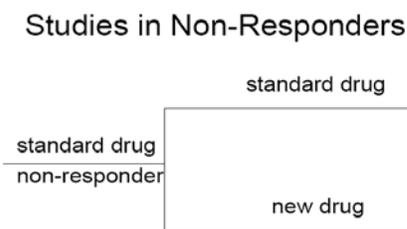
1086
1087 Knowing that a drug is effective in patients who have not responded to, or who have responded
1088 inadequately, to other therapy is an important clinical finding. The lack of apparent response to prior
1089 treatment, however, is not a reliable predictor of how the patient would respond in a new setting (i.e.,
1090 in a new randomized trial). It is therefore usually essential, in order to demonstrate effectiveness of
1091 the new drug in non-responders, to randomize patients to both the failed drug and the test drug (Figure
1092 6) because in most cases it cannot be assumed that the non-responders to the other therapy outside the
1093 trial will not respond to it in the setting of the new trial, as the examples in Section V illustrate. There
1094 are cases in which previous non-response will almost certainly be repeated (e.g., non-response to an
1095 oncologic treatment) so that re-randomization to the failed treatment may not be necessary. Great care
1096 should be taken in reaching this conclusion, however, as the altered conditions in a new study might
1097 affect the response to an apparently failed prior treatment (e.g., by improving compliance). It would,
1098 therefore, be important to ensure that the failed therapy was properly administered. Finally, it should

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1099 be appreciated that re-randomization to a failed treatment could pose significant ethical problems in a
1100 serious or life-threatening condition.

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Figure 6

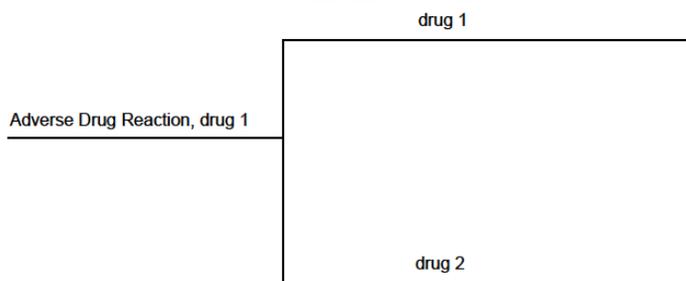


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4. *Studies in Patients Intolerant of a Prior Treatment*

As in the case of studies of non-responders, knowing that patients who have experienced important adverse effects on an available therapy do not have such effects on a new agent is a clinically important finding. In this case, too (as in studies of non-responders), it is critical to randomize to the poorly tolerated previous therapy and the new drug (Figure 7) to reach a conclusion that the new drug has superior safety, because the adverse effects do not always reappear when a treatment is repeated. For the same reason, it would also be advisable to include a placebo group to be certain that the side effect was indeed reproduced in the previous treatment group. This study design is not feasible if the adverse effect was dangerous to the patient. In that case, showing that a new drug lacks the side effect is probably feasible only in a trial in a previously untreated population, unless it is possible to know very confidently that the adverse effect would have recurred in the previously treated population that did not tolerate the initial treatment (i.e., use of a historically controlled design).

Figure 7
Studies in Intolerants



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C. Type I Error Rate Control for Enriched Study Subpopulations

Generally, even if patients both with and without an enrichment characteristic are studied, the primary endpoint is expected to be driven by the result in the enriched subgroup. In some enrichment designs that enroll patients both with and without the enrichment characteristic, the type-I error rate for the study can be shared between a test conducted using only the enriched subpopulation and a test conducted using the entire population.⁵² This alpha allocation scheme allows for assessment of the treatment effect in the entire entered population when there may be some effect in the patients without the enrichment characteristic while also allowing the assessment in the enriched subgroup. Determining the required sample size that will provide reasonable power to test the different hypotheses while controlling type-I error (usually including a pre-specified order of testing or a multiple testing procedure allowing testing of both hypotheses) is challenging.

D. Adaptive Enrichment

Although an enrichment characteristic should almost always be specified before a study begins, certain adaptive designs⁵² can use enrichment strategies that identify predictive markers during the course of the study. Specifically, entry criteria or sample size can be modified for later stages of a trial if factors can be identified that increase event rate or treatment response (e.g., discovery that the enrichment factor has a greater impact on response than anticipated or that the patients without the enrichment factor have a very low response or safety concern). Such changes will need appropriate type-I error rate control to account for interim, unblinded analyses of the accumulating data as well as type-I error allocation if there were analyses of multiple subgroups, but adjustment may not be needed for the enrichment if all randomized patients are included.^{53,54} However, the issue of whether the statistical testing results obtained by such an adaptive enrichment strategy are reproducible needs to be addressed. For a full discussion of adaptive designs see FDA’s draft Adaptive Design Guidance.⁵²

During a trial, information may be obtained from accruing patients that could inform a pre-planned opportunity for modification of the trial’s size or design (e.g., to be certain that the enriched population is of adequate size). In a trial that enrolls patients with and without enrichment factors, the relevant sample size would generally be based on the number of subjects entered with the enrichment characteristic, so that sample size adjustment based on a blinded analysis of the proportion of marker-positive patients would usually be recommended. It is possible for enrichment to occur to a greater degree in the later stages of a trial. For example, a broader population might be studied initially with altered entry criteria implemented in later stages of the trial based on interim results. Such a procedure should be described in the study protocol, and the analysis should adequately account for the changes. A number of examples of such trials have been reported in the literature, but there is little experience as yet with their use in drug development.

Although there has been little practical experience with enriched study designs whose sample size changes after the start of the study, or where other changes in the design are pre-planned to be based on accrued information during a trial, a number of adaptive designs seem potentially applicable:

1. In a study that includes both marker-positive and negative patients, an interim look could reveal, either on an early endpoint (e.g., imaging or PD biomarker or tumor response rate) or

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1172 later endpoint (e.g., progression-free survival) that the marker-negative population has a much
1173 lower response than the marker-positive group. Additional enrollment of marker-negative
1174 patients could be reduced or stopped entirely.

1175 2. The design could be used to obtain more precise information on the performance
1176 characteristics of a classifier, for example, by examining an early endpoint using several
1177 different classifier cut-offs to determine the optimal cut-off value. If a cut-off proved too low
1178 (i.e., selected a population with few responses), it could be raised. Such plans would need to
1179 be carefully specified in advance as part of the phase 3 study, but could also be examined in
1180 exploratory studies.

1181 3. When the optimal marker cutpoint is not well known prior to the study, use of several different
1182 cut-offs creates multiplicity issues; cut-offs should be pre-specified or corrected for the
1183 multiple choices. Jiang, Friedlin, and Simon have suggested a study design that tests the
1184 treatment effect in the overall population and in a subset defined by a marker cut-off point
1185 when the cut-off point is determined after the study is over using a statistical procedure that
1186 controls for multiplicity.⁵⁵

1187 4. Interim analyses could suggest changing entry criteria to emphasize a better-responding
1188 subgroup; if all randomized patients were included in the final analysis, such a step would not
1189 appear to need alpha adjustment, although describing results could be challenging.⁵³ It should
1190 be appreciated, however, that unplanned adjustments of entry criteria based on early data can
1191 have unexpected effects that may not enhance the ability of the study to show an effect.

1192 5. Sample size planning in these designs can be difficult, because such designs are generally used
1193 when there is uncertainty about the prevalence of a marker, its predictiveness, and what sample
1194 size or entry criteria adjustments are contemplated. In some more complex situations, use of
1195 statistical simulations may help calculate study power and the impact of design choices.

1196

1197 **E. Cautions in Interpretation**

1198

1199 Any use of an enrichment design should be explicit in the protocol and study report and should fully
1200 detail the rationale, specific enrichment maneuvers, and their impact on interpretation of results. For
1201 example, if only half of the patients screened passed the entry test, that should be noted, and the
1202 impact of this selection in terms of the expected response rate in the overall population and on the
1203 generalizability of the results should be evaluated. The importance of such descriptions is obvious for
1204 trials in which high-risk patients (prognostic enrichment) and probable responders (predictive
1205 enrichment) have been selected, where the description is critical to knowing to which patients the
1206 results apply, but such descriptions are important for all types of enrichment studies. Given the
1207 potentially complex interpretation of studies using enrichment designs, we strongly recommend early
1208 discussions with the Agency on plans to use them.

1209

1210 When enrichment depends on a proteomic or genetic test, particularly if the test is intended for use in
1211 practice to identify patients to be treated, the analytical validity of the test is critical. In addition to
1212 assay validity, for any marker used to select patients, even a familiar one, its sensitivity and specificity
1213 and positive and negative predictive values should be well characterized. To the extent an enrichment
1214 strategy successfully identifies patients with high event rates or high response rates and leads to a
1215 successful study, study results could be said to speak for themselves (i.e., the randomized trial *did*

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1216 show an effect; the event rate *was* high enough) and certainly support the effectiveness of the drug in
1217 the population studied. Again, however, the enrichment strategies should be clearly described to
1218 indicate how the drug is to be used and to whom the results might apply (groups of patients that do and
1219 do not benefit).

1220
1221 Selection of the optimal predictive enrichment study design, specifically, whether to include both
1222 marker-positive and negative patients, and whether to introduce adaptive elements can be difficult to
1223 determine in the face of uncertainty about the properties of the enrichment marker. Many publications
1224 have addressed these issues.^{41,50,51,53} One conclusion is that the greater the uncertainty regarding the
1225 marker cut-off and responsiveness of marker-negative patients, the more sense it makes to include a
1226 reasonable sample of marker-negative patients, perhaps using an adaptive design to exclude such
1227 patients if they are seen not to respond. In general, especially when marker prevalence in the
1228 population studied is relatively low, it would generally be sensible to stratify by marker status.

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1231 **VII. ENRICHMENT – REGULATORY ISSUES**

1232

1233 **A. Summary – The Decision to Use an Enrichment Strategy**

1234

1235 The decision to use an enrichment design is largely left to the sponsor of the investigation, but like the
1236 entire research and clinical communities, FDA is very interested in targeting treatments to the people
1237 who can benefit from them (i.e., individualization). FDA’s interests also include the adequacy of the
1238 study (Will it successfully assess effectiveness in a defined population and, in so doing, support
1239 marketing approval?) as well as the degree to which study findings can be described in drug labeling.

1240

1241 As discussed above, there are many reasons to use such designs, including an enhanced benefit–risk
1242 relationship if a population with an increased likelihood of response can be identified, and efficiency
1243 in drug development, as smaller studies can often be used to demonstrate effectiveness. There are,
1244 however, two critical considerations when contemplating the use of enrichment designs.

1245

1246 *1. Can the Enrichment Strategy Be Used to Identify the Patients to Whom the Drug*
1247 *Should Be Given?*

1248

1249 When patients with an increased likelihood of response can be defined before treatment by a predictive
1250 marker (a pathophysiologic or genomic characteristic, a short-term screen such as response to a test
1251 dose), a straightforward method is available for selecting patients for treatment. In contrast, some
1252 empiric strategies that provide predictive enrichment (e.g., studying known responders in a
1253 conventional study or in a randomized withdrawal study) can efficiently establish the effectiveness of
1254 a drug in a subset of the population, but provide no way for prescribers to prospectively identify
1255 patients with a greater likelihood of response, or predict the magnitude of response in an unselected
1256 patient. Although this type of untargeted treatment may seem troubling (treatment of many to attain a
1257 response in only some), the reality is that this is generally the case with treatments that are approved
1258 on the basis of conventional studies in a non-enriched population, where there is typically a wide range
1259 of responses, including no effect at all, or even harm in some cases. However, it needs to be
1260 understood and made clear that the magnitude and/or likelihood of a treatment response for an
1261 unselected patient could be substantially less than the mean response observed in a clinical trial that

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1262 employed an empiric enrichment strategy. When the prescriber is reasonably able to gauge the
1263 effectiveness of a drug in an individual patient (e.g., pain is relieved, cholesterol is reduced), the pre-
1264 treatment ability to predict the likelihood of a drug response with accuracy may not be as critical.

1265
1266 In some cases, enrichment cannot be used to select patients for study because the enrichment factor is
1267 not known until after the treatment is initiated, but is used to identify the subset of the studied
1268 population to be analyzed – for example, the patients with a sensitive organism in studies of
1269 antimicrobial drugs. Again, the subset analysis documents effectiveness, but the treated population, at
1270 least initially, will be the unselected patients (i.e., a larger group than the population of potential
1271 responders). Such situations are unavoidable, however, if treatment is urgent and must be initiated
1272 before the enrichment measure is available.

1273
1274 Finally, the quality (sensitivity and specificity) of the enrichment strategy may not be critical to
1275 knowing that a drug has an effect in the study subjects (if the selected study population shows an
1276 effect, the drug was in fact effective), but it is important to therapeutic use, as it is plainly undesirable
1277 to inadvertently include non-responders and exclude potential responders because the test has poor
1278 precision or because cut-off points were poorly selected.

1279
1280 The above problems noted, however, if the enrichment strategy allows a drug of value to be developed
1281 and shown to be effective when disease and response variability would make non-enriched studies
1282 unable or unlikely to succeed, there is clearly an important gain from such strategies. Labeling will
1283 reflect limitations and concerns, but it seems clear that a drug shown effective in an enriched study
1284 should be available even if the responder population is not identified as precisely as would be
1285 desirable.

1286 2. *Might the Drug Be Useful in a Broader Population Than Was Studied?*

1287
1288 The data that should be obtained for the marker-negative patients will be considered below, but it can
1289 be anticipated that less information will be available about them and there will be greater uncertainty
1290 as to their response to the treatment. Studies in unselected patients (i.e., a non-enriched population),
1291 the typical basis for drug approval, simply ignore the question of identifying responders and lead to
1292 treatment of many patients who will not benefit. There would thus seem to be a gain from a process
1293 that seeks to establish the characteristics that predict a drug response, rather than ignoring the varied
1294 responses and overcoming them by simply increasing sample sizes.

1295
1296 In general, then, FDA is prepared to approve drugs studied primarily or even solely in enriched
1297 populations and will seek to ensure truthful labeling that does not overstate either the likelihood of a
1298 response or the predictiveness of the enrichment factor. But the extent of data that should be available
1299 on the non-enriched subgroup should always be considered. Postmarket commitments or requirements
1300 may be requested to better define the full extent of a drug's effect (including efficacy and safety
1301 studies and trials in a broader population).

1302
1303 **B. Data That Should Be Obtained for the Marker-Negative Patients**

1304
1305 Well-controlled enrichment studies, if successful, provide clear evidence of effectiveness in the
1306 population studied. In many cases, however, questions will remain as to how to identify the patients to

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1307 which the data apply and the magnitude of effect in the marker-negative patients. In general, the
1308 heterogeneity-reducing efforts raise few problems of this kind, but the prognostic and, especially, the
1309 predictive enrichment strategies do raise them, and the remedies before or even after approval are not
1310 always clear and may be circumstance-specific.

1311
1312 For studies of serious or irreversible endpoints, showing an effect in a high-risk population (e.g., high
1313 blood pressure, high LDL with a history of MI, severe CHF) has, historically, been a prelude to later
1314 demonstrations of effects in lower-risk patients, but the effect size has sometimes been smaller (CHF),
1315 the endpoints have sometimes changed (mortality versus composite in the lower risk patients), and
1316 consequently, benefit–risk considerations may change. FDA has generally accepted the results from
1317 prognostically enriched studies, approved a claim based on the observed effect, and described the
1318 study, including the patient population, in the Clinical Studies section of labeling, with any enrichment
1319 selection criteria noted. The specific patient population studied has sometimes, but certainly not
1320 always, been given as the indicated population in the Indications section of labeling in addition to its
1321 description in the Clinical Studies section.

1322
1323 The most challenging situation is a finding of benefit in a clinically, demographically,
1324 pathophysiologically, proteomically, or genetically selected population used for predictive enrichment,
1325 because in that case there is inevitably the question of how sure we are that other patients could not
1326 benefit, even if the benefit were smaller. Ideally, therefore, there will be at least some data on the
1327 marker-negative population; the study designs in Figure 5 illustrate this approach, but it must be
1328 appreciated that a study, if sized to show an effect in the enriched population, will have relatively little
1329 capacity to detect or rule out the anticipated substantially smaller effect in the marker-negative
1330 population. Nevertheless, the design does provide some information on that population. It could, for
1331 example, show that the estimated treatment effect is not likely to be as large in the marker-negative
1332 population, but could show a trend suggesting a smaller effect.

1333
1334 In deciding how much information should be available on the marker-negative population, both before
1335 and after approval, risk–benefit assessments of several kinds should be considered. When the
1336 treatment is a critical advance for the enriched group, it would generally be unreasonable to delay
1337 approval for the enriched group, even if few data on the group without the enrichment factor were
1338 available and even if some off-label use were anticipated despite appropriate labeling (although how
1339 much off-label use would be unacceptable would depend on the expected risk of the treatment). For
1340 less important benefits, factors considered would include the expected risks to the marker-negative
1341 population from the use of the drug (related to its observed toxicity), the relative size of the marker-
1342 positive and marker-negative populations, and how convincing it is that there is no useful treatment
1343 effect in the marker-negative population, so that labeling and other information might make off-label
1344 use unlikely. If the risks of the drug are substantial, FDA will want greater confidence that patients
1345 who will not benefit from the drug will not be treated in the course of patient care. Conversely, if the
1346 risks appear low, less assurance regarding the marker-negative population would be sufficient.
1347 Ironically, a very important medical benefit (e.g., survival or prevention of significant disability), one
1348 that realistically and ethically cannot be delayed, could raise the greatest concerns because there would
1349 be great desire to use the drug in the marker-negative population. During development it is important
1350 to discuss with FDA review staff how much information should be available before drug approval.

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1352 *Note:* The information on the marker-negative group could come from all of the studies in the clinical
1353 program, including both studies in an unselected population and studies in the marker-negative
1354 population. The information that will describe the effect in the marker-negative group includes direct
1355 empirical evidence of clinical results in patients, pathophysiologic information, or combinations of
1356 various kinds of information.

1357
1358 A number of considerations would support collection of less (sometimes even no) information on the
1359 non-enrichment-factor population (again, this should always be discussed with FDA review staff):

- 1360
1361 • A clear pathophysiologic basis for concluding that the non-enriched population will not
1362 respond (e.g., because they lack the molecular target of the drug or because they cannot
1363 convert a pro-drug to its active metabolite); this could be supported by pre-clinical or clinical
1364 pharmacologic and biomarker studies
- 1365 • Early clinical studies that show very marked difference in response between the enrichment
1366 and non-enrichment populations.

1367 Important toxicity such that use in a less responsive population, even if a small effect could be present,
1368 would not be attractive.

1369
1370 **D. Labeling**

1371
1372 The use of enrichment designs will often have implications for labeling, especially the Indications and
1373 Usage, Dosage and Administration, and Clinical Studies sections. As noted above, prognostic
1374 enrichment will be described in Clinical Studies and has sometimes led to a description of the studied
1375 population in Indications. Use of predictive enrichment will usually lead to an indication directed at
1376 the predictive enrichment population, often with recommended testing, and a description of the
1377 selection in clinical studies. If no marker-negative patients are studied, it will be difficult to describe
1378 the effect of enrichment fully. In some cases, however, earlier data may show clearly that the marker-
1379 negative patients cannot respond. In general, significant toxicity would lead to stronger direction
1380 toward the marker-positive patients and strong directions to avoid the marker-negative patients. When
1381 an enrichment design results in the need for an approved or cleared companion diagnostic device,
1382 coordinated labeling for the therapeutic product and the diagnostic device should be provided.^{55,56}

APPENDIX

Additional Guidance Related to Enrichment

A number of Agency guidances have been issued that provide additional and related information about clinical trial designs (including enrichment designs) and demonstrating effectiveness. See especially the following draft and final guidances. Once finalized the draft guidances will represent FDA's thinking on their respective topics.

Agency guidances are available at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

- FDA's draft guidance *Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies* focuses particularly on use and evaluation of genomic strategies in early drug development, and highlights identification of enrichment options for later trials.
- FDA's draft guidance for industry and FDA staff on *In Vitro Companion Diagnostic Devices*⁵⁶ defines IVD (in vitro diagnostic) companion diagnostic devices that are essential for the safe and effective use of their corresponding therapeutic products. The draft guidance describes the Agency's policies for approval and clearance and for labeling companion diagnostics, contemporaneously with approval and labeling of the therapeutic product.
- FDA's draft guidance *Adaptive Design Clinical Trials for Drugs and Biologics*⁵² considers the case of enrichment approaches introduced only after randomization and based on interim evaluations. Such a retrospective finding would have to be carefully implemented and highly compelling to be accepted without further study.
- FDA's guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*⁵⁷ describes the amount and type of evidence needed to demonstrate effectiveness, and is applicable to studies using enrichment designs.

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