
Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (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) Lee Pai-Scherf at 301-796-3400 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

**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)
Oncology Center of Excellence (OCE)**

**September 2018
Procedural**

Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

and/or

*Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002*

*Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

**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)
Oncology Center of Excellence (OCE)**

**September 2018
Procedural**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	MASTER PROTOCOL DEFINITION AND POTENTIAL OPPORTUNITIES AND CHALLENGES	3
	A. Description and Concept of Master Protocols.....	3
	B. Potential Opportunities and Challenges Posed by Master Protocols.....	3
IV.	TYPES OF MASTER PROTOCOLS.....	4
	A. Single Investigational Drug or Investigational Drug Combination Across Multiple Cancer Populations	4
	B. Investigational Drugs or Investigational Drug Combination(s) in Single Cancer Type.....	5
	C. Other Trial Designs.....	6
V.	SPECIFIC DESIGN CONSIDERATIONS IN MASTER PROTOCOLS	6
	A. Use of a Single Common Control Arm.....	6
	B. Novel Combination of Two or More Investigational Drugs.....	6
	C. Studies With Drugs Targeting Multiple Biomarkers	7
	D. Adding and Stopping Treatment Arms	7
	E. Independent Data Monitoring Committee	8
VI.	BIOMARKER DEVELOPMENT CONSIDERATIONS	8
VII.	STATISTICAL CONSIDERATIONS	9
	A. Nonrandomized, Activity-Estimating Design	9
	B. Randomized Designs.....	9
	C. Master Protocols Employing Adaptive/Bayesian Design	9
	D. Master Protocols With Biomarker-Defined Subgroups	10
VIII.	SAFETY CONSIDERATIONS	10
	A. Safety Monitoring and Reporting Plans	10
	B. Independent Safety Assessment Committee	11
	C. Institutional Review Board/Independent Ethics Committee	12
	D. Informed Consent Document.....	13
IX.	ADDITIONAL REGULATORY CONSIDERATIONS	13
X.	CONTENT OF A MASTER PROTOCOL	14
	A. New IND Submission	14
	B. Amendments to the Master Protocol.....	15
XI.	COMMUNICATION AND INTERACTIONS WITH FDA.....	15

APPENDIX..... 17

1 **Master Protocols: Efficient Clinical Trial Design Strategies to**
2 **Expedite Development of Cancer Drugs and Biologics**
3 **Guidance for Industry¹**
4
5

6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
12

13
14
15 **I. INTRODUCTION**
16

17 This guidance provides recommendations to sponsors of drugs or biologics for the treatment of
18 cancer regarding the design and conduct of clinical trials intended to simultaneously evaluate
19 more than one investigational drug² and/or more than one cancer type within the same overall
20 trial structure (master protocols) in adult and pediatric cancers. In general, the recommended
21 phase 2 dose (RP2D) has been established for an investigational drug or drugs evaluated in a
22 master protocol.
23

24 This guidance is intended to serve as advice and a focus for continued discussions among FDA,
25 pharmaceutical sponsors, the academic community, and the public.³
26

27 This guidance describes aspects of master protocol designs and trial conduct and related
28 considerations, such as biomarker codevelopment and statistical analysis considerations, and
29 provides advice on the information that sponsors should submit to FDA and on how sponsors can
30 interact with FDA to facilitate efficient review.
31

32 This guidance does not cover FIH clinical trials using expansion cohorts to expedite drug
33 development. FDA addresses that topic in the draft guidance for industry *Expansion Cohorts:*

¹ This guidance has been prepared by the Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research in cooperation with the Oncology Center of Excellence and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² For the purpose of this guidance, the term *drug* refers to human drugs and biological products.

³ In addition to consulting guidances, sponsors are encouraged to contact the review division to discuss specific issues that arise during drug development.

34 *Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and*
35 *Biologics.*⁴
36

37 This guidance does not address all issues relating to clinical trial design, statistical analysis, or
38 the biomarker development process. Those topics are addressed in the International Conference
39 on Harmonisation (ICH) guidances for industry *E9 Statistical Principles for Clinical Trials* and
40 *E10 Choice of Control Group and Related Issues in Clinical Trials* and the guidance for industry
41 and FDA staff *In Vitro Companion Diagnostic Devices.*⁵
42

43 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
44 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
45 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
46 the word *should* in Agency guidances means that something is suggested or recommended, but
47 not required.
48

49 **II. BACKGROUND**

50
51
52 There is increased interest in expediting late-stage drug development through developing trial
53 designs that test multiple drugs and/or multiple cancer subpopulations in parallel under a single
54 protocol, without a need to develop new protocols for every trial. The term *master protocol* is
55 often used to describe the design of such trials, with variable terms such as *umbrella*, *basket*, or
56 *platform* describing specific designs. Examples of trials using master protocols include the Lung-
57 MAP trial (NCT02154490), the NCI-MATCH trial (EAY131, NCT02465060),⁶ [see Figures B
58 and C in the Appendix], and the Pediatric MATCH trial (APEC1621, NCT03155620)] In
59 contrast to traditional trial designs, where a single drug is tested in a single disease population in
60 one clinical trial, master protocols use a single infrastructure, trial design, and protocol to
61 simultaneously evaluate multiple drugs and/or disease populations in multiple substudies,
62 allowing for efficient and accelerated drug development.
63

64 Because of the complexity of these trials evaluating multiple drugs and/or disease populations
65 and the potential regulatory impact, it is important that such trials be well designed and well
66 conducted to ensure patient safety and to obtain quality data that may support drug approval.
67
68

⁴ When final, this guidance will represent FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁵ See also the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* and the draft guidances for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* and *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, these guidances will represent the FDA’s current thinking on these topics.

⁶ See information on this trial at the National Cancer Institute web page at <https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?id=NCT02465060&r=1>.

69 **III. MASTER PROTOCOL DEFINITION AND POTENTIAL OPPORTUNITIES AND**
70 **CHALLENGES**

71
72 **A. Description and Concept of Master Protocols**
73

74 For the purpose of this guidance, a master protocol is defined as a protocol designed with
75 multiple substudies, which may have different objectives and involves coordinated efforts to
76 evaluate one or more investigational drugs in one or more disease subtypes within the overall
77 trial structure. In general, FDA strongly recommends that the sponsor establish the RP2D for the
78 investigational drug(s) before evaluation using a master protocol. Individual drug substudies
79 under the master protocol can incorporate an initial dose-finding phase, for example, in pediatric
80 patients when sufficient adult data are available to inform a starting dose and the investigational
81 drug provides the prospect of direct clinical benefit to pediatric patients.⁷
82

83 A master protocol may be used to conduct the trial(s) for exploratory purposes or to support a
84 marketing application and can be structured to evaluate, in parallel, different drugs compared to
85 their respective controls or to a single common control. The sponsor can design the master
86 protocol with a fixed or adaptive design⁸ with the intent to modify the protocol to incorporate or
87 terminate individual substudies within the master protocol. For examples of types of master
88 protocols, see section IV., Types of Master Protocols.
89

90 **B. Potential Opportunities and Challenges Posed by Master Protocols**
91

92 The potential advantage of a master protocol is flexibility and efficiency in drug development,
93 consistent with FDA's goal of helping to make safe and effective drugs and drug combination
94 treatments available to the public. A master protocol provides an opportunity to incorporate
95 efficient approaches, such as a shared control arm and/or the use of centralized data capture
96 systems to enhance efficiency. However, a master protocol also can create challenges in the
97 conduct and analysis of the trial that, if not properly addressed, can increase risk to patients or
98 delay the development of the drug.
99

100 Examples of potential challenges include the following:
101

- 102 • Difficulty in attribution of adverse events to one or more investigational drugs can occur
103 when multiple drugs are administered within various arms and the trial lacks a single
104 internal control for those drugs.
105
- 106 • With multiple drugs being studied across multiple protocols and investigational new drug
107 applications (INDs), assessing the safety profile of any given investigational drug is
108 difficult.
109

⁷ 21 CFR 50 subpart D.

⁸ See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, this guidance will represent FDA's current thinking on this topic.

- The presence of multiple study groups allows potential *overinterpretation* of findings, resulting in delays in drug development. For example, a biomarker-defined subpopulation could be identified, because of multiple comparisons, as a responder population based on ad hoc between-arm comparisons that prove to be false.

IV. TYPES OF MASTER PROTOCOLS

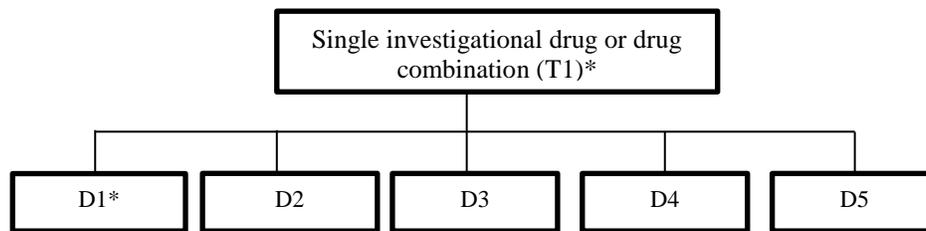
This section provides examples of types of master protocols and considerations related to their designs. FDA strongly recommends that all investigational drugs evaluated in a master protocol undergo preliminary dose-finding FIH trials with the RP2D of each investigational drug established before evaluation in a master protocol.

FDA strongly encourages sponsors to discuss with the review division plans to develop drugs under a master protocol early in the development program to obtain feedback on the design of such a protocol before the submission.

A. Single Investigational Drug or Investigational Drug Combination Across Multiple Cancer Populations

A master protocol designed to test a single investigational drug or drug combination in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics is commonly referred to as a *basket trial* (shown in Figure 1).

Figure 1: Schematic Representation of a Master Protocol With *Basket Trial* Design



* T = investigational drug; D = protocol defined subpopulation in multiple disease subtypes.

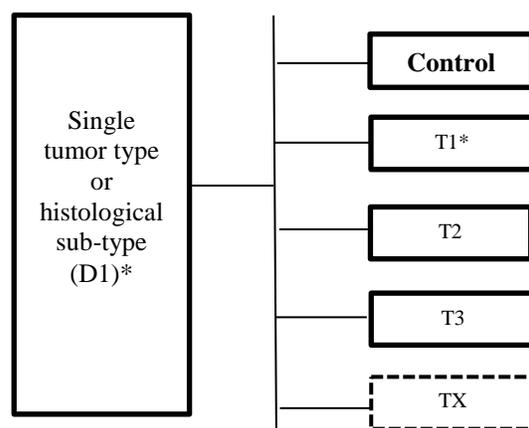
The substudies within basket trials are usually designed as single-arm activity-estimating trials with overall response rate (ORR) as the primary endpoint. A strong response signal seen in a substudy may allow for expansion of the substudy to generate data that could potentially support a marketing approval. Each substudy should include specific objectives, the scientific rationale for inclusion of each population, and a detailed statistical analysis plan (SAP) that includes sample size justification and stopping rules for futility. For specific aspects related to design and analysis related to a master protocol for a basket trial, see sections V., Specific Design Considerations in Master Protocols, and VII., Statistical Considerations.

156 An example of a master protocol with *basket trial* design is the phase 2 trial evaluating
157 vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations⁹ (see Figure A in the
158 Appendix).

160 B. Investigational Drugs or Investigational Drug Combination(s) in Single 161 Cancer Type

162
163 A master protocol designed to evaluate multiple investigational drugs administered as single
164 drugs or as drug combinations in a single disease population are commonly referred to as
165 *umbrella trials* (shown in Figure 2). Substudies within umbrella trials can include dose-finding
166 components to identify safe doses of an investigational drug combination before proceeding with
167 an activity-estimating component. As previously stated, the sponsors should ensure the RP2D for
168 each investigational drug has been established before evaluation in a master protocol.

169
170 **Figure 2: Schematic Representation of a Master Protocol with *Umbrella Trial* Design**



171
172
173
174
175
176
177
178
179
180
181
182
183
184 * T = investigational drug; D = protocol defined subpopulation in single disease subtypes; TX = dotted border
185 depicts future treatment arm.

186
187 Umbrella trials can employ randomized controlled designs to compare the activity of the
188 investigational drug(s) with a common control arm. The drug chosen as the control arm for the
189 randomized substudy or substudies should be the standard of care (SOC) for the target
190 population, and this may change over time if newer drugs replace the SOC. For specific aspects
191 related to design and analysis related to a master protocol for an umbrella trial, see sections V.
192 Specific Design Considerations in Master Protocols, and VII., Statistical Considerations).

193
194 An example of a master protocol with umbrella trial design is the original version of the LUNG-
195 MAP trial,¹⁰ a multidrug, multi-substudy, biomarker-driven trial in patients with
196 advanced/metastatic squamous cell carcinoma of the lung. Eligible patients were assigned to
197 substudies based on their biomarkers or to a *nonmatch* therapy substudy for patients not eligible

⁹ Hyman DM et al., 2015, "Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations, N Engl J Med, 373(8):726-736.

¹⁰ Herbst RS et al., 2015, Lung Master Protocol (Lung-MAP)- A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400, Clin Cancer Res,21(7):1514-1524.

198 for the biomarker-specific substudies. Within the substudies, patients were randomized to a
199 biomarker-driven target or to SOC therapy (see Figure B in the Appendix).

200

201 **C. Other Trial Designs**

202

203 Master protocol designs may also incorporate design features common to both *basket* and
204 *umbrella* trials and may evaluate multiple investigational drugs and/or drug combination
205 regimens across multiple tumor types.

206

207 An example of a master protocol with a complex trial design is the NCI-MATCH trial,¹¹ which
208 aims to establish whether patients with one or more tumor mutations, amplifications, or
209 translocations in a genetic pathway of interest identified in solid tumors or hematologic
210 malignancies derive clinical benefit if treated with drugs targeting that specific pathway in a
211 single-arm design (see Figure C in the Appendix).

212

213

214 **V. SPECIFIC DESIGN CONSIDERATIONS IN MASTER PROTOCOLS**

215

216 **A. Use of a Single Common Control Arm**

217

218 FDA recommends that a sponsor use a common control arm to improve efficiency in master
219 protocols where multiple drugs are evaluated simultaneously in a single disease (e.g., umbrella
220 trials). FDA recommends that the control arm be the current SOC so that the trial results will be
221 interpretable in the context of U.S. medical practice. Changes in SOC for the target population
222 can occur during the conduct of the trial, because of either a new drug approval or new scientific
223 evidence, making it no longer ethical to randomize patients to the previous SOC. In that case, the
224 sponsor should suspend patient enrollment until the protocol, the SAP, and the protocol informed
225 consent document are modified to include the new SOC as control.

226

227 In general, comparative analyses may be conducted only between a test drug and the common
228 control and not between experimental treatment arms (for statistical considerations in the use of
229 common control, see section VII., Statistical Considerations).

230

231 **B. Novel Combination of Two or More Investigational Drugs**

232

233 In master protocols with substudies intended to evaluate concomitant administration of two or
234 more investigational drugs, the sponsor should provide strong scientific rationale for the use of
235 the drug combination regimen. FDA strongly recommends that the sponsor ensures the RP2D
236 has been identified for each individual drug in all cases where each drug may have antitumor
237 activity.

238

239 The master protocol should summarize available safety, pharmacology, and preliminary efficacy
240 data for each investigational drug; the biological rationale for use of the drugs in combination
241 rather than use of an individual drug; and evidence, if any, of synergy when used in combination.

¹¹ Abrams J et al., 2014, National Cancer Institute's Precision Medicine Initiatives for the New National Clinical Trials Network, Am Soc Clin Oncol Educ Book:71-6, doi: 10.14694/EdBook_AM.2014.34.71.

242 In some instances, the master protocol may include a dose-finding component for novel
243 combinations where the RP2D of the combination regimen has not been established. Safety data
244 from a minimum of six patients treated at the proposed dosage for the drug combination regimen
245 should be available before proceeding with the efficacy evaluation. If such an approach is
246 considered in a pediatric population, sponsors should ensure that the full relevant age range of
247 pediatric patients is covered and the investigational drug provides the prospect of direct clinical
248 benefit to pediatric patients.¹² The sponsor should submit results of the dose-finding phase for
249 FDA review before proceeding with the efficacy phase.

250
251 For clinical development programs designed to evaluate combinations of two or more
252 investigational drugs, it is essential that the general investigational plan describe the approach to
253 demonstrating the contribution of each investigational drug to the observed treatment effect to
254 support a risk-benefit assessment.¹³

255 **C. Studies With Drugs Targeting Multiple Biomarkers**

256
257 FDA strongly recommends early discussion of biomarker development plans when the sponsor
258 plans to use one or more biomarkers to inform patient selection for trials. For master protocols
259 with drugs targeting multiple biomarkers, it is essential that patient selection tests be analytically
260 validated with well-defined criteria for marker positivity before initiation of the trial.
261

262
263 In master protocols containing substudies with drugs that target multiple biomarkers, the
264 protocol should contain a prespecified plan for allocation of patients who are potentially eligible
265 for more than one substudy. Patient allocation and sample size assumptions for each randomized
266 substudy should take into consideration the potential prognostic implications of specific
267 biomarkers.

268
269 For additional information, see section VI., Biomarker Development Considerations and VII.,
270 Statistical Considerations.

271 **D. Adding and Stopping Treatment Arms**

272
273 Master protocols evaluating multiple investigational drugs can add, expand, or discontinue
274 treatment arms based on findings from prespecified interim analyses or external new data.¹⁴
275

276
277 Before initiating the trial, the sponsor should ensure that the master protocol and its associated
278 SAP describe conditions that would result in adaptations such as the addition of a new
279 experimental arm or arms to the trial, reestimation of the sample size based on the results of an
280 interim analysis, or discontinuation of an experimental arm based on futility rules.

¹² 21 CFR 50 subpart D.

¹³ See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* and the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

¹⁴ See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, this guidance will represent FDA's current thinking on this topic.

281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317

E. Independent Data Monitoring Committee

If results from one or more substudies are anticipated to form the basis of a marketing application, the master protocol should describe and provide the charter for an independent radiologic review committee to perform blinded tumor-based assessments. In addition, the protocol should describe and provide a charter for an independent data monitoring committee (IDMC) to monitor the efficacy results. The IDMC charter should authorize the committee to conduct prespecified and ad hoc assessments of efficacy and futility and recommend protocol modifications or other actions, including sample size adjustment and discontinuation or modification of a substudy based on futility or overwhelming evidence of efficacy.

The responsibilities of the IDMC can be limited to assessment of efficacy with another committee responsible for the assessment of safety (e.g., an independent safety assessment committee (ISAC)). The IDMC can also be structured to perform both functions. Pediatric expertise should be provided on IDMCs that will review pediatric studies, and an ethicist should be considered for all studies. For additional responsibilities related to safety monitoring, see section VIII.B., Independent Safety Assessment Committee.

VI. BIOMARKER DEVELOPMENT CONSIDERATIONS

Master protocols evaluating biomarker-defined populations should explain why use of the biomarker is appropriate and employ in vitro diagnostic (IVD) tests that are analytically validated. Use of IVDs with inadequate analytical performance characteristics (e.g., precision, accuracy) may produce unreliable results with respect to performance of the drug. Protocols with IVD tests that are not analytically validated can be placed on clinical hold for deficiencies in design to meet the stated objectives.¹⁵

Sponsors should establish procedures for sample acquisition, handling, and the testing and analysis plans as early as possible in the biomarker development program. The sponsor may need to submit the IVD’s analytical validation data for FDA to determine whether the clinical results will be interpretable.

Further, when the trial uses an investigational IVD, the sponsor and institutional review boards (IRBs) should assess what investigational device application¹⁶ requirements apply¹⁷ using the criteria found in 21 CFR 812.2 that address level of risk that the device presents to trial subjects

¹⁵ 21CFR 312.42(b)(2)(ii).

¹⁶ 21 CFR 812.

¹⁷ See the guidance for sponsors, clinical investigators, IRBs, and FDA staff *FDA Decisions for Investigational Device Exemption Clinical Investigations* and the guidance for IRBs, clinical investigators, and sponsors *IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE Is Needed*.

318 (i.e., significant risk, nonsignificant risk).¹⁸ Sponsors can contact the appropriate center at FDA
319 (the Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation
320 and Research (CBER)) for the device, or sponsors can submit all information regarding the
321 oncology codevelopment program, including IVD information in the IND submitted to the
322 Center for Drug Evaluation and Research (CDER) or CBER, to seek trial risk determination.¹⁹
323

324 A sponsor interested in pursuing the development of a specific biomarker test for marketing as a
325 device should consult the appropriate center at FDA (CDRH or CBER) responsible for review of
326 the IVD.
327

328 **VII. STATISTICAL CONSIDERATIONS**

329 **A. Nonrandomized, Activity-Estimating Design**

330
331
332
333 In nonrandomized protocols, where the primary endpoint is ORR, the planned sample size
334 should be sufficient to rule out a clinically unimportant response rate based on the lower bound
335 of the 95 percent confidence interval around the observed response rate. The analysis plan should
336 describe the futility analyses to be conducted. FDA recommends designs such as the Simon two-
337 stage design²⁰ that limit exposure to an ineffective drug. If a sponsor anticipates that the results
338 would form the primary basis of an efficacy claim in a marketing application, the clinical
339 protocol and SAP should ensure that collected data are of adequate quality for this purpose.
340 Additionally, the SAP should prespecify the timing of the final analysis, ensure adequate data
341 collection and follow-up on all patients for efficacy and safety, and describe the plan for
342 independent review of confirmed ORR in solid tumors for each substudy. If preliminary results
343 from a substudy or substudies suggest a major advance over available therapy, the sponsor
344 should meet with the review division to discuss modifications to the protocol.
345

346 **B. Randomized Designs**

347
348 If a sponsor incorporates randomization into an umbrella trial design, FDA strongly recommends
349 use of a common control arm when possible.
350

351 **C. Master Protocols Employing Adaptive/Bayesian Design**

352
353 In master protocols that incorporate adaptive designs, the SAP should provide all information
354 described in the guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*

¹⁸ See the draft guidance for industry, FDA staff, sponsors, and IRBs *Investigational IVDs Used in Clinical Investigations of Therapeutic Products*. When final, this guidance will represent FDA's current thinking on this topic.

¹⁹ See the draft guidance for industry *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination*. When final, this guidance will represent the FDA's current thinking on this topic.

²⁰ Simon R, 1989, Optimal Two-Stage Designs for Phase II Clinical Trials, *Control Clin Trials*, 10(1):1-10.

355 and the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval*
356 *of Human Drugs and Biological Products*²¹ and describe plans for futility analyses.²² Master
357 protocols can use a Bayesian statistical method or other methods for planning or modifying the
358 sample size, dropping an arm, or other adaptive strategies. The SAP should include details on
359 implementation of Bayesian or other methods.

360

361 **D. Master Protocols With Biomarker-Defined Subgroups**

362

363 In master protocols with basket or complex design, where patient assignment to a treatment arm
364 is based on the presence of a specific biomarker of interest, the protocol should clearly specify
365 how patients with more than one biomarker of interest will be assigned to substudies. There are
366 two approaches to making such assignments that FDA considers acceptable from a clinical trial
367 design perspective, but other approaches may also be appropriate. One approach is to prioritize
368 biomarkers or treatments. For example, in the BATTLE-1 trial,²³ investigators ranked the
369 biomarker groups based on their predictive values and assigned patients with multiple
370 biomarkers to the group for one of their biomarkers that has the highest predictive value. The
371 other approach is based on a prespecified randomization ratio. For example, the Lung-MAP
372 trial¹⁰ uses a reversed ratio of prevalence rates. Using reverse prevalence ratios, patients in the
373 trial with tumors that have biomarkers with low prevalence have a greater likelihood to be
374 assigned to a substudy for the lower prevalence population.²⁴

375

376

377 **VIII. SAFETY CONSIDERATIONS**

378

379 **A. Safety Monitoring and Reporting Plans**

380

381 The sponsor is required to ensure proper monitoring of the investigations and to ensure that the
382 investigations are conducted in accordance with the general investigational plan and protocols
383 contained in the IND.²⁵

384

385 The sponsor should establish a systematic approach that ensures rapid communication of serious
386 safety issues to clinical investigators and regulatory authorities under IND safety reporting

²¹ When final, this guidance will represent the FDA’s current thinking on this topic.

²² See also the ICH guidance for industry *E9 Statistical Principles for Clinical Trials* and the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

²³ Kim ES et al., 2011, The BATTLE Trial: Personalizing Therapy for Lung Cancer, *Cancer Discov*, 1(1): 44–53.

²⁴ See the draft guidance for industry *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease*. When final, this guidance will represent FDA’s current thinking on this topic.

²⁵ 21 CFR 312.50. See the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring*.

387 regulations.²⁶ In addition, the approach should describe the process for rapid implementation of
388 protocol amendments to address serious safety issues.²⁷
389

390 The original IND (see section IX., Additional Regulatory Considerations) should contain a
391 proposed plan for periodic submissions of a cumulative summary of safety, as described under
392 21 CFR 312.32(c)(3), which is more frequent than annually.²⁸ The summary of safety should
393 include information on any action taken for safety reasons for each investigational drug during
394 that reporting period across the clinical development program for the investigational drug. The
395 sponsor should reference the most recent cumulative safety report in support of protocol
396 amendments proposing modification of existing or new substudies.
397

398 Given the complexity of and the generally rapid accrual to these trials, resulting in increased
399 risks to patients of failure to promptly identify adverse events, sponsors should select medical
400 monitors who have training and experience in cancer research and in the conduct of clinical
401 trials, so that safety information can be promptly assessed.
402

403 **B. Independent Safety Assessment Committee** 404

405 For all master protocols, the sponsor should institute an ISAC or an IDMC structured to assess
406 safety in addition to efficacy. The sponsor should describe in the IND the constitution of this
407 committee and the definition of its responsibilities. The committee should complete the real-time
408 review of all serious adverse events as defined in FDA regulations and periodically assess the
409 totality of safety information in the development program.²⁹ The ISAC or IDMC should have
410 responsibility for conducting prespecified and ad hoc assessments of safety to recommend
411 protocol modifications or other actions including but not limited to the following:
412

- 413 • Discontinuing or modifying a substudy based on safety information obtained from the
414 protocol or from information external to the trial
415
- 416 • Changing the eligibility criteria if the risks of the intervention appear to be higher in a
417 particular subgroup
418
- 419 • Altering the drug dosage and/or schedule if the adverse events observed appear likely to
420 be mitigated by such changes
421
- 422 • Instituting screening procedures that could identify those subjects at increased risk of a
423 particular adverse event
424

²⁶ 21 CFR 312.32.

²⁷ 21 CFR 312.30(b)(1) and 312.30(b)(2)(ii).

²⁸ 21 CFR 312.32.

²⁹ 21 CFR 312.32.

- Identifying information needed to inform current and future trial subjects of newly identified risks via changes in the informed consent document and, if appropriate, recommending re-consent of current subjects to continue trial participation.

C. Institutional Review Board/Independent Ethics Committee

A sponsor must not initiate a clinical trial until an IRB or independent ethics committee has reviewed and approved the protocol and the trial remains subject to continuing review by an IRB.³⁰ Once approved, the investigator should provide cumulative safety information to the IRB along with other information required by the IRB to allow the IRB to meet its requirements.³¹

Because of the complexity of master protocols, in general, the sponsor is expected to conduct assessment of safety more frequently than on an annual basis and to provide this information to the investigator. Sponsors are required to “keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use.”³² The investigator must convey this information to the IRB during the time of the IRB’s continuing review, or sooner, if the information is an unanticipated problem involving risk to human subjects or others.³³ This information can include a description of the detailed plan for timely, periodic communication of trial progress; cumulative safety information; and other reports from the ISAC or IDMC. This information is necessary to allow the IRB to evaluate, for example, the risks to patients of the ongoing investigation and the adequacy of the informed consent document.

To facilitate IRB review of master protocols, FDA recommends the use of a central IRB.³⁴ The central IRB should have adequate resources and appropriate expertise to review master protocols in a timely and thorough manner. When necessary, an IRB can invite individuals with competence in special areas (i.e., consultants) to assist in the review of complex issues that require expertise beyond or in addition to that available on the IRB.³⁵

Given the rapid accumulation of safety data and the complexity of the trial design, IRBs should consider convening additional meetings (i.e., ad hoc meetings of an existing IRB) to review the evolving safety information, provided regulatory requirements in 21 CFR part 56, such as quorum, can be met. Alternatively, a separate, duly constituted specialty IRB can be established and specifically charged with meeting on short notice to review new information and/or modifications to trials with master protocols. Such an IRB would need to satisfy the same

³⁰ 21 CFR 56.103(a).

³¹ 21 CFR 56.109(f) and 21 CFR 312.66.

³² 21 CFR 312.55(b).

³³ See 21 CFR 312.66 and the guidance for clinical investigators, sponsors, and IRBs *Adverse Event Reporting to IRBs — Improving Human Subject Protection*.

³⁴ 21 CFR 56.114. See the guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials*.

³⁵ 21 CFR 56.107(f).

460 requirements of any IRB (i.e., 21 CFR part 56); however, it could be designed to facilitate a
461 quorum by keeping membership to a minimum (i.e., 21 CFR 56.107 requires that each IRB have
462 at least five members) and being composed of experienced members who are capable of meeting
463 and reviewing trial-related materials on short notice. Ad hoc meetings of an existing IRB or the
464 establishment of a separate specialty IRB designed to facilitate the review of trials with master
465 protocols are acceptable approaches that, if appropriately constituted and operated, can satisfy
466 the regulatory requirement for IRB oversight.

467
468 Irrespective of the type of IRB that is used, if the master protocol includes plans to enroll
469 pediatric patients in the trial, we recommend the IRB include (either as a member or an invited
470 nonvoting expert) an individual or individuals who have expertise in the management of
471 pediatric oncology patients and experience with the regulatory requirements, including parental
472 permission and assent requirements, for the enrollment of pediatric patients in clinical
473 investigations.³⁶

474 475 **D. Informed Consent Document**

476
477 In addition to submitting informed consent documents to the IRB for review, the Sponsor may
478 need to submit the original and all updated informed consent documents to the IND to allow
479 FDA to assess that patients have the information to make informed decisions regarding
480 participation in the trial.

481
482 In addition to new safety information, updates to the informed consent document should include
483 all clinically important protocol modifications. Protocol amendments submitted under 21 CFR
484 312.30 should be accompanied by the revised informed consent documents unless immediate
485 modifications are needed for patient safety, in which case the sponsor should submit the revised
486 informed consent document as soon as possible.

487 488 489 **IX. ADDITIONAL REGULATORY CONSIDERATIONS**

490
491 Because of the complexity of master protocols and the need to avoid miscommunication that
492 could compromise patient safety, sponsors should submit each master protocol as a new IND to
493 FDA. For INDs that contain master protocols, sponsors should consider the following:

- 494
495 • The master protocol should be the only trial that is conducted under the IND.
- 496
497 • The sponsor should submit the master protocol(s) to the review division in CDER or
498 CBER responsible for reviewing the primary indication(s). If more than one indication is
499 being investigated, the sponsor should submit the IND to the most appropriate clinical
500 review division within the Office of Hematology and Oncology Products in CDER,
501 taking into account the population to be studied, or to CBER.

502
503
³⁶ 21 CFR 50 subpart D.

504 **X. CONTENT OF A MASTER PROTOCOL**

505

506 **A. New IND Submission**

507

508 Master protocols are subject to all the requirements under 21 CFR 312. To ensure that all
509 required aspects are complete, a master protocol should contain the required elements for clinical
510 protocols described in 21 CFR 312.23(a)(6)(iii) and all the information described in sections V,
511 VI, VII, and VIII of this guidance. Specifically, the protocol and IND submission should address
512 the following elements:

513

514 • Core elements as required per 21 CFR 312.20-23

515

516 • Submission in electronic (electronic common technical document (eCTD)) format

517

518 • Appropriate letters of authorization for each investigational drug

519

520 • Suggested IND title as “PROTOCOL NAME: List of investigational drugs” (e.g.,
521 LUNG-MAP: Drug X, Drug Y, Drug Z)

522

523 • Submission of each substudy within the same IND under a separate folder in Section
524 5.3.5. of the eCTD (as shown in Figure D in the Appendix) to facilitate review

525

526 • Inclusion of a list of all the substudies in Section 5.2 of the eCTD, in addition to the
527 master protocol title (as shown in Figure E in the Appendix)

528

529 The master protocol should also include the following:

530

531 • A detailed description of the trial design as text and as a visual depiction

532

533 • Procedures for sample acquisition, handling, and testing of biomarkers, as appropriate

534

535 • Prominent identification of all substudies

536

537 • Description of all groups responsible for monitoring patient safety (e.g., IRB, ISAC,
538 IDMC).

539

540 • Description of the plan for submission of interim safety and efficacy results

541

542 • The proposed informed consent document

543

544 **B. Amendments to the Master Protocol**

545
546 Protocol amendments that substantively affect the safety or scope of the master protocol should
547 contain the following:³⁷

- 548
- 549 • A clean and tracked changes version of the amended master protocol document
 - 550
 - 551 • A list of the proposed changes in tabular format with the rationale for each proposed
552 change and the following supportive information, if available:
553
 - 554 – Summary of available safety and efficacy data
 - 555
 - 556 – New nonclinical toxicology or pharmacology data and clinical data as appropriate to
557 support the protocol modification
 - 558
 - 559 – An updated informed consent document
 - 560

561 In general, to facilitate communications and expedite the drug development program, FDA
562 recommends that a sponsor submit a substudy for disease-specific development to a new IND
563 reviewed by the appropriate disease-specific team, particularly when that team is located in
564 another review division. In such instances, the sponsor should cross-reference to the original
565 IND information on common elements (e.g., description of groups responsible for monitoring
566 patient safety) rather than resubmit the information with the substudy.

567

568

569 **XI. COMMUNICATION AND INTERACTIONS WITH FDA**

570

571 Sponsors should consult guidances for industry for best communication practices³⁸ and
572 meetings³⁹ with FDA to ensure open lines of dialogue before and during the drug development
573 process. With regard to master protocols, sponsors should consider the following:

- 574
- 575 • FDA strongly encourages a sponsor to request a pre-IND meeting. This can allow the
576 sponsor and FDA to reach key agreements on the design and conduct of the protocol.
577
 - 578 • The cover letter for all meeting requests should clearly state “REQUEST FOR
579 MEETING-MASTER PROTOCOL (Meeting Type).”
580

³⁷ See 21 CFR 312.30(d) and 312.31(b) for content and format requirements for protocol amendments and information amendments.

³⁸ See the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*.

³⁹ See the draft guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* and *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. When final, this guidance will represent the FDA’s current thinking on this topic.

- 581
- 582
- 583
- 584
- 585
- 586
- 587
- 588
- 589
- 590
- 591
- 592
- 593
- 594
- 595
- 596
- 597
- The sponsor should notify the regulatory project manager via secure email or a phone call 48 hours before submitting any protocol amendment that substantively affects the safety or scope of the protocol.
 - The cover letter for such protocol amendments should be clearly marked as “Protocol Amendment-MASTER PROTOCOL.”
 - If the amendment contains changes needed to eliminate an apparent immediate hazard to subjects (e.g., closure of a substudy for unacceptable toxicity, modification of eligibility or monitoring to mitigate the risks), the sponsor *should implement immediately* the revised protocol. The sponsor should ensure that FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 21 CFR 56.104(c).⁴⁰ For other substantive changes that affect safety, scope, or the scientific quality of the study, the cover letter should contain a statement that the revised protocol will not be initiated until 30 days after submission to the IND to allow FDA to assess the risks of the proposed change and until the change has been approved by the IRB.⁴¹

⁴⁰ 21 CFR 312.30(b)(2)(ii).

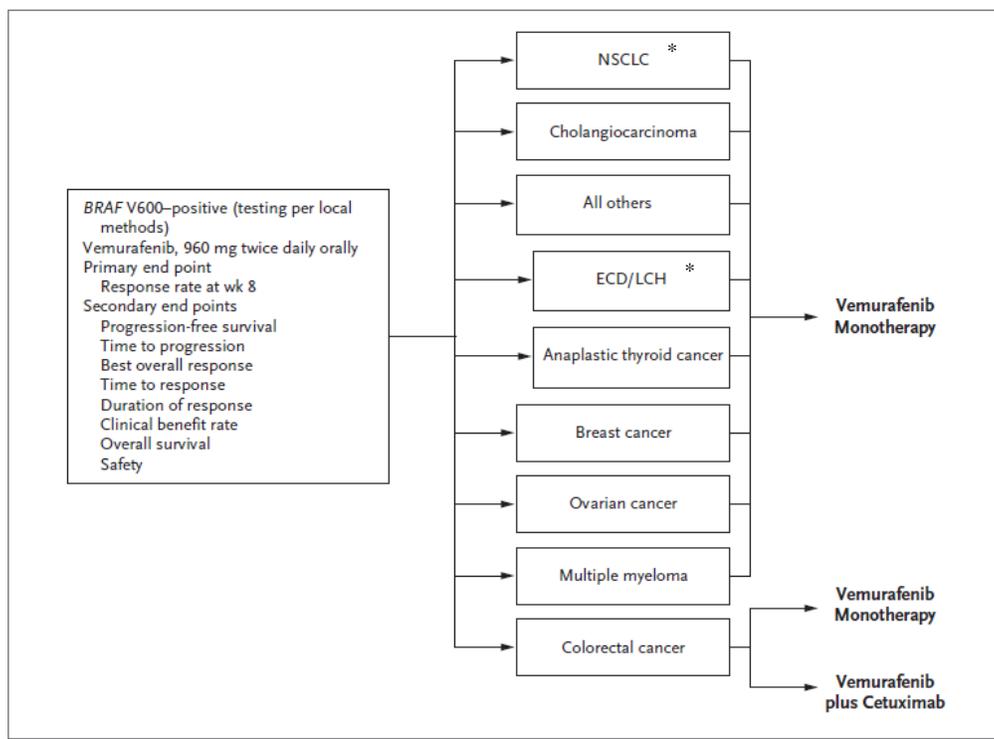
⁴¹ 21 CFR 312.30(b)(2)(i)(b).

598 **APPENDIX**

599
600 **Example of a Master Protocol With a Basket Trial Design**

601
602 An example of a master protocol with basket design is the phase 2 trial evaluating vemurafenib
603 in multiple nonmelanoma cancers with BRAF V600 mutations, as shown in Figure A.

604
605 **Figure A: Vemurafenib in Nonmelanoma Cancers Harboring BRAF V600 Mutations¹**



606
607 *NSCLC = Non-small cell lung cancer; ECD = Erdheim-Chester disease; LCH = Langerhans cell histiocytosis.

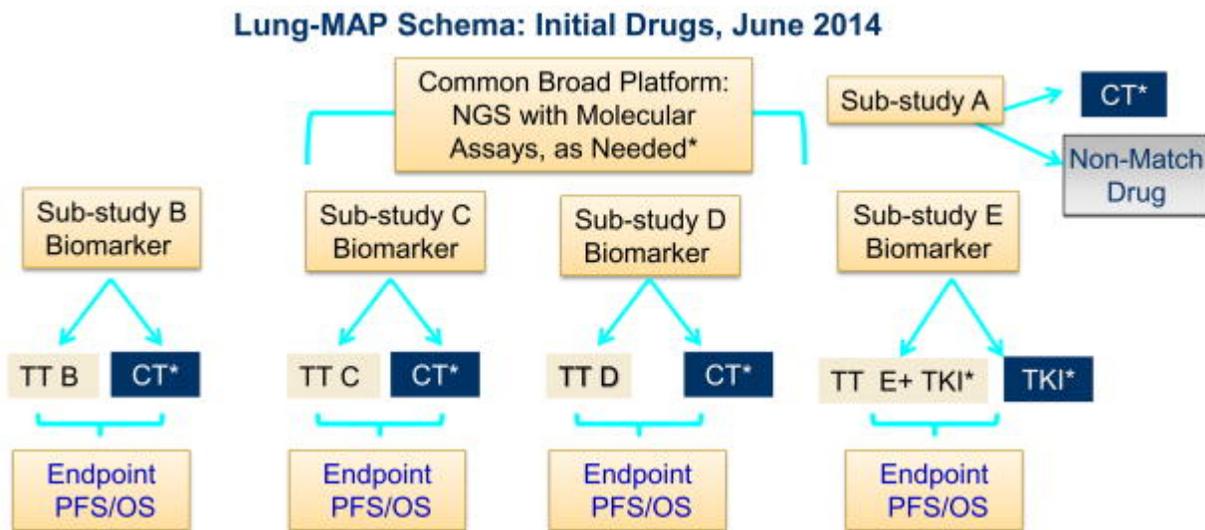
¹ Hyman DM et al., 2015, "Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations, N Engl J Med, 373(8):726-736.

608 **Example of a Master Protocol With an Umbrella Trial Design**

609
610 An example of a master protocol with an umbrella design is the original version of the LUNG-
611 MAP trial, a multidrug, multi-substudy, biomarker-driven trial in patients with
612 advanced/metastatic squamous cell carcinoma of the lung, as shown in Figure B.
613

614 **Figure B: LUNG-MAP Trial in Patients With Squamous Cell Carcinoma of the Lung²**

615



616
617 *Archival formalin-fixed, paraffin-embedded tumor, fresh core needle biopsy if needed. NGS = next generation
618 DNA sequencing; OS = overall survival; PFS = progression free survival; TT = targeted therapy; CT =
619 chemotherapy (docetaxel or gemcitabine); TKI = tyrosine kinase inhibitor (erlotinib).
620

² Herbst RS et al, 2015, Lung Master Protocol (Lung-MAP)- A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400, Clin Cancer Res,21(7):1514-1524.

621 **Example of a Master Protocol With a Complex Trial Design**

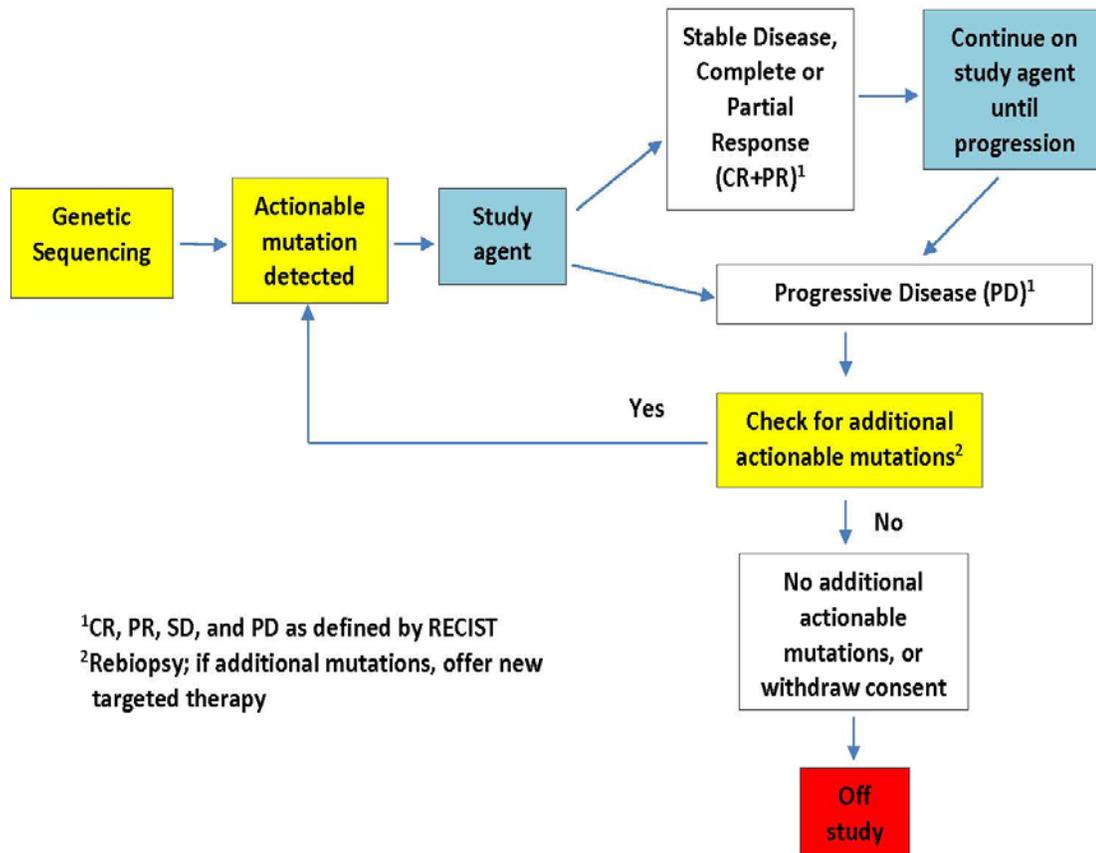
622

623 An example of a master protocol with a complex trial design is the NCI-MATCH trial, as shown
624 in Figure C.

625

626

Figure C: National Cancer Institute Match Trial Scheme³



627 * RECIST = response evaluation criteria in solid tumors.

628

³ Adapted from Abrams J et al., 2014, National Cancer Institute's Precision Medicine Initiatives for the New National Clinical Trials Network, Am Soc Clin Oncol Educ Book: 71-6, doi: 10.14694/EdBook_AM.2014.34.71.

629 **Examples of How to Use eCTD for a Master Protocol**

630

631 Figure D (below) gives an example of how a sponsor can submit each substudy within the same
632 investigational new drug application under a separate folder in section 5.3.5. of the electronic
633 common technical document (eCTD).

634

635 **Figure D: Schematic Figure of eCTD with an IND with Master Protocol “CANCER 123”**
636 **and Substudies S-1, S-2, S-3, and S-4***

637

- 1. Regional
- 2. Common Technical Document Summaries
- 5. Clinical Study Reports
 - 5.2 Tabular Listing of all Clinical Studies
 - Tabular Listing of All Clinical Studies
 - 5.3.5. Reports of Efficacy and Safety Studies [Indication]
 - 5.3.5.2 CANCER
 - 5.3.5.2.1 CANCER 123 – Master Protocol CANCER 123
 - 5.3.5.2.2 CANCER 123- S 1 – Drug X – Biomarker XX
 - Protocol or Amendment
 - Protocol Amendment version 1 – 01Jan2020
 - Protocol Amendment version 1 – Tracked Changes
 - Protocol Amendment version 3 – Summary of Changes
 - IEC IRB Consent Form List
 - 5.3.5.2.3 CANCER 123- S 2 – Drug Y – Biomarker YY
 - 5.3.5.2.4 CANCER 123- S 3 –Drug Z – Biomarker ZZ
 - 5.3.5.2.5 CANCER 123- S 4 – Drug W – Biomarker WW

638

639 * eCTD = electronic common technical document; IND = investigational new drug application.

640

641 Figure E (below) gives an example of how a sponsor can include a list of all the substudies in
642 section 5.2 of the eCTD, in addition to the master protocol title.

643

644 **Figure E: Module 5.2 of eCTD Tabular Listing of All Clinical Studies and Substudies***

645

Study Identifier	Location of Study	Objectives of the Study	Study Design and type of control	Test products, Dosage regimen, Route of Administration	No. of subjects or diagnosis of patients	Healthy subjects or diagnosis of patients	Duration of Treatment	Study status; type of report
Master CANCER123								
CA123-S1								
CA123-S2								
CA123-S3								
CA123-S4								

646 * eCTD = electronic common technical document.