

Draft ASHP Guidelines on Appropriate Off-Label Medication Use

1 **Purpose**

2 The American Society of Health-System Pharmacists (ASHP) believes that prescribing,
3 dispensing, and administration of drug products for off-label medication use often represents a
4 therapeutic approach that has been extensively studied and is supported by the medical
5 literature. Drug therapy decisions of healthcare professionals and patients should not be
6 limited by third-party reimbursement standards that are based solely on FDA-approved drug
7 products and their subsequent labeling. Instead, some degree of flexibility must be maintained
8 in order optimize patient outcomes and allow for individualized care. While the ultimate
9 responsibility for the safety and efficacy of off-label use resides with the prescriber, the hospital
10 or health-system's pharmacy and therapeutics (P&T) committee, policy and procedures, and
11 pharmacists should all take part in managing and supporting off-label medication use. The
12 ultimate goal is to improve patient access to the most appropriate, efficacious treatment for
13 each patient and their disease.

14 Off-label usage applies to any use of a medication in a manner including the diagnosis,
15 combination with other medications, dosage, frequency, route of administration, line of
16 therapy, or age of the patient that is not specifically approved by the FDA and delineated on the
17 label given to the drug during the approval process.¹ It is common for the drug products'
18 labeling to fail to represent the most current therapeutic information.² This can be attributed to
19 several factors. 1) Any changes to the approved FDA label for a medication must be submitted
20 to the FDA by the manufacturer and this can be a time consuming and expensive process. 2)

21 The body of medical knowledge is constantly expanding including publications demonstrating
22 the value of medications in settings other than the original FDA approved labeling. 3) Legally,
23 prescribers are not limited to FDA labeled indications when making the best therapeutic
24 decision for their patients. Therefore, in many clinical situations, off-label use represents the
25 most appropriate therapy for patients. Failure to recognize these circumstances or, more
26 importantly, regarding such uses as unapproved or experimental, may restrict patient access to
27 necessary drug therapies. However, distinction must be made between evidence-based off-
28 label use and the inappropriate use of off-label drugs. By definition, evidence-based off-label
29 use demands the support of clinical trials and case reports. In contrast, inappropriate off-label
30 use has little or no literature support. Inappropriate use of off-label drugs must be avoided due
31 to efficacy and safety concerns resulting from the drug bypassing any risk-benefit analysis.³ In
32 addition to the limitations of FDA approved indications, there are also limitations to guidelines
33 and standards of practice recommendations produced by professional organizations. This is due
34 primarily to the constant influx of new literature resulting in the continual evolution of
35 standards of practice, making it difficult for professional societies to review scientific data
36 expediently and develop standards that remain absolutely current.

37 **Impact of Off Label Medication Use**

38 When discussing off-label medication use, the site of care must be considered due to variation
39 in prevalence and urgency. For example, inpatient situations related to the treatment of life-
40 threatening conditions or end-organ damage will require more immediate action than more
41 general inpatient or outpatient situations. For infused medications, certain settings and

42 particular populations demand more prevalent use of off-label treatment regimens. These
43 include oncology, rare diseases and pediatric practices which have a tendency to exhibit
44 patterns of off-label drug usage.^{4,5} Targeted therapies have increased off label usage in
45 oncology due to the supporting science and clinical benefits demonstrated for the same target
46 in multiple cancer types. Furthermore, oral medications and injectable medications for self-
47 administration by the patient in a home setting often lack direct oversight by a clinical
48 pharmacist, relying on payer scrutiny and off-label justification by the dispensing pharmacist. In
49 contrast, infusion and specialty medications given in the hospital setting demand pharmacist
50 oversight and further involvement in the off-label process. Differences by payer limit the
51 utilization of off-label medications in all settings, basing their coverage decisions on levels of
52 criteria including approved compendia listings, payer specific clinical policies, or submission of
53 peer-reviewed evidence based literature. It is important to consider that payer policies do not
54 always reflect what is medically necessary for the individual patient, indicating the need for a
55 structured off-label medication use process within each institution.

56 **Recommendations**

57 ***Use of P&T Guidelines.*** The P&T committee should be considered the arbiter of institutional
58 policies regarding off-label medication use and should rely on scientific evidence to guide its
59 decisions.⁶ When considering off-label use, supporting safety and efficacy evidence must be
60 carefully evaluated and a risk–benefit determination made, especially when alternatives with
61 FDA-approved labeling are available. The P&T committee should implement a systematic
62 approach to evaluating evidence and benefits before approval of off-label drug therapy.

63 Furthermore, when the off-label use of a drug product is expected to occur frequently, the P&T
64 committee should consider establishing protocols guiding that use in order to expedite the
65 process, especially when the potential benefits and harms are difficult and time-consuming to
66 quantify.

67 ***Use of Formulary Restrictions.*** Formulary management should include selection of medications
68 that optimize patient care and outcomes while also curbing unnecessary off-label usage. In the
69 inpatient setting, restrictions for non-formulary medications and approval requirements before
70 administration protect the institution from financial loss due the lack of a separate structure for
71 reimbursement of medications (except in rare situations where carve outs exist). In the
72 outpatient setting, the implementation of a restrictive formulary and increased payer scrutiny
73 should further limit unnecessary off-label usage. In either case, both inpatient or outpatient use
74 of medication that falls outside of the approved formulary or lacks the appropriate evidence
75 based support, should undergo a formal review process including a peer review of medical
76 necessity and evaluation of patient safety. Consideration should be given to restricting all
77 outpatient infused specialty and high dollar medications to their FDA approved indications
78 when added to the formulary. Doing so ensures that an off-label process is initiated with every
79 use that falls outside of the FDA approved indication.

80 ***Defined Off-Label Policy and Practice.*** With the introduction of newer, expensive specialty
81 agents that are being prescribed in various disease states, the propensity to use medication
82 outside the label poses a significant financial risk in addition to the patient care risks outlined

83 above. The implementation of an off-label protocol mitigates the risk of payment denial,
84 informs patients of their payment responsibility and helps to ensure fiscal viability of the
85 practice. Development of specific criteria is necessary and should take into consideration the
86 medication, duration, utilization and monitoring of the treatment. The rationale for usage
87 should be documented and supported and the patient should be educated and consented if
88 warranted. It is pertinent that the prescriber who is considering the use of a medication for an
89 off-label indication have a face-to-face discussion of the off-label clinical and financial benefits
90 and risks with the patient, document that conversation within the medical record, and have the
91 patient sign an Advanced Beneficiary Notice (ABN) or Notice of Non Coverage (NONC) as
92 applicable.

93 The cost of a medication is a significant consideration whether it will be administered in
94 the outpatient or inpatient setting; however, the outpatient reimbursement structure for most
95 payers provides for expensive medications to be separately reimbursed (unlike the inpatient
96 setting, where a set payment or DRG is all that will be reimbursed, despite the costs of the
97 individual medications administered). For commercial and Medicare Advantage patients in the
98 outpatient setting a pre-determination should be conducted to gain approval for off-label use
99 prior to the patient receiving the medication. This is also true for commercial or Medicare
100 Advantage patients in the inpatient setting who will need continuation of their therapy in the
101 outpatient setting. For payers who do not provide a process for pre-determination (traditional
102 Medicare and Medicaid), guidance from CMS National and Local Coverage Determinations
103 (NCD/LCD), CMS approved drug compendia, or CMS peer reviewed literature should be
104 referenced to ensure the necessary level of support. In some cases, commercial payers publish

105 their own clinical guidelines and policies which should be referenced as well, but most follow or
106 closely align to the requirements outlined by CMS. In both situations, access to the off-label
107 treatment should be dependent upon NCD/LCD support, the presence of the indication on one
108 of the CMS approved compendia, or sufficient peer review evidence (two Phase II or one Phase
109 III study). Detailed algorithms that outline an example off-label medication policy differentiated
110 by payer can be found in Appendix B.

111 ***Use of Internal Peer Review.*** A more rigorous process for approval should be implemented in
112 the case of innovative off-label medication use, in which the prescriber's requested treatment
113 is based upon reasonable rationale but lacking sufficient supporting evidence related to safety,
114 efficacy, and cost-effectiveness.⁷ In these cases, an escalation process should exist within the
115 institution or practice that provides for existing literature, case reports and pertinent clinical
116 patient information to be submitted for peer review to a disease-specific leader or a division
117 director. If the reviewer(s) determines that there is insufficient evidence to support the
118 requested use, the use of the medication is not recommended and other alternatives should be
119 considered.⁸

120 ***Reconsideration Request.*** Medicare claims for off-label use are more likely to be denied, when
121 compared to commercial payers, due to the lack of an existing pre-determination process.
122 However, CMS allows for a formal process for requesting revisions to current policy and
123 guidelines unrelated to any single patient treatment if deviations from the evidence or standard
124 of practice are identified with Medicare.⁹ Submitted requests should demonstrate safety and

125 benefit to a patient population through inclusion of peer-reviewed literature (phase II or III
126 trials and patient cases may be considered) and thorough explanation of how the current
127 coverage deviates from the literature. When applicable, examples of other payer policies such
128 as a commercial payer or an LCD in a different region that include the requested coverage
129 should be referenced as additional support. Formal requests can be submitted for both NCD
130 and LCD, however the NCD reconsideration process is more rigorous and time-consuming as
131 they often require open comment periods. Requests for changes in commercial payer policies
132 and clinical guidelines should follow an identical approach.

133 ***Pharmacists at the Point of Care.*** ASHP believes that health-system pharmacists bear
134 responsibility for ensuring optimal patient outcomes from all drug therapy and therefore
135 should play a significant role in respect to off-label use. When embedded in the patient care
136 team, pharmacists can assist in determining the appropriateness of the medication use and
137 providing the supportive information when medications are prescribed outside of the defined
138 scope of the FDA label. Pharmacists, in collaboration with the patient care team, can provide
139 the financial team with all the information necessary to begin the pre-determination process.

140 ***Use of Manufacturer/Reimbursement Support Services.*** When specialty, high cost, infused and
141 injectable medications are prescribed for an off-label indication, it is essential to know a
142 patient's pharmacy and medical insurance coverage and the availability of assistance programs
143 for the prescribed medication. Because benefits will vary based on site of care, distinction
144 should be made between the pharmacy benefit plan and medical benefits when determining

145 coverage. Reimbursement support services provided by many manufacturers help the patient
146 to understand their out of pocket cost share and provide information on the availability of
147 manufacturer copay assistance or foundation copay assistance support. In the event that the
148 off label use results in an insurance denial, some pharmaceutical manufacturers also offer
149 assistance with the appeal process. In addition, some pharmaceutical companies may provide
150 the patient with free medication if the patient meets both the clinical and financial
151 requirements to qualify for their program. It is recommended to have dedicated pharmacy staff
152 available to assist patients in navigating and accessing these resources. Since some companies
153 will ship replacement or free drug directly to the institution for patients who qualify, it is also
154 important to ensure these drugs will be received directly by pharmacy personnel. Lastly, it is
155 important to note that not all pharmaceutical companies will provide assistance outside of the
156 FDA approved usage, so reliance solely on these programs to provide support is not
157 recommended.

158 ***Request for External Peer Review.*** Most commercial payers provide for the opportunity of a
159 peer to peer discussion between the attending physician and a peer physician employed by the
160 payer (or hired as a consultant) when a predetermination request for an off label use of a
161 medication has been denied. It affords an opportunity for the attending physician to speak with
162 a medical director or physician reviewer about the denial. By requesting this conversation, the
163 attending physician can share critical clinical information or rationale that may not have been
164 adequately conveyed by the pre-determination and emphasize the opportunity for an outcome
165 that is supported by the published data. Peer to peer discussions are most effective when the

166 physician reviewer is an expert in the specialty for which the indication is intended to be used.
167 Organizations requesting to schedule a peer to peer discussion should be specific and request a
168 physician specialist familiar with the disease for which the medication is intended to treat.

169 ***Pharmacists as Reimbursement Experts.*** In addition to their value at the point of care in
170 supporting the safe and effective use of off-label medications, it is also important to employ
171 pharmacists who understand all aspects of medication reimbursement and the revenue cycle.
172 This includes knowledge of payer policies and payer approval processes, use of medication
173 assistance programs, understanding of clinical guidelines, reconsideration packet preparation,
174 an understanding of the appeals process for drug denials, etc. Most important to these roles is
175 the ability to bridge the clinical and financial worlds, a critical skill to ensure appropriate
176 reimbursement for off-label medication use. These experts stay current with the changing
177 healthcare landscape of both governmental and commercial plans to ensure financial success
178 when infused and specialty medications are administered. They attend Payer Relations
179 meetings, gathering important information regarding upcoming changes and addressing
180 specific payment concerns encountered with specific patients or groups of patients. They are
181 critically important for their ability to translate timely payer and policy requirements to the
182 administrative and front line pharmacy staff to ensure receipt of appropriate reimbursement
183 for the services provided.

184 **Conclusion**

185 With the rate at which scientific evidence is evolving, specialty areas such as oncology,

186 neurology, dermatology and others will continue to be challenged with off-label medication
187 use. The “personalization” of therapies will further contribute to the growth of off-label use as
188 biomarkers are identified in patients with a disease not covered by the initial FDA approved
189 indication. ASHP acknowledges that off-label medication use often represents the best choice
190 of therapy for a patient and their disease. By implementing an off-label medication use policy
191 that incorporates our best practice guidelines, institutions will improve patient access to the
192 most efficacious treatment options, ensure patient safety and reduce financial risk to the
193 patient and the institution.

194 **Appendix A**

195 **Advanced Beneficiary Notice (ABN):** a written notice which a physician or designee must
196 provide a patient with Original Medicare that informs the patient that Medicare may not pay
197 for the medication and that the patient may be responsible for payment if the claim is denied.
198 An ABN should be issued prior to the patient receiving an item or service.¹⁰

199 **Appeal:** the process used when a party (for example, a beneficiary, provider, or supplier)
200 disagrees with an initial determination or a revised determination for health care items or
201 services. For example, an appeal can be initiated after denial of a claim, in which insurance
202 company or carrier refuses to honor the request of a payer or individual to pay for healthcare
203 services provided by a healthcare provider.

204 **CMS Approved Compendia:** a reference that serves as a comprehensive listing of FDA-
205 approved drugs and biologicals and is recognized as an authoritative source when determining

206 medically-accepted indications for off-label use. The five compendia listed as well as the
207 requirements to be identified as medically accepted evidence by Medicare are listed as:

208 ***Elsevier Gold Standard Clinical Pharmacology***: if narrative text is supportive

209 ***American Hospital Formulary Service (AHFS) Drug Information***: if narrative text is
210 supportive

211 ***Truven Health Analytics Micromedex DrugDex***: if indication is Class I, IIa, IIb

212 ***National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium***: if
213 indication is Category 1 or 2a

214 ***Wolters Kluwer Lexi-Drugs***[®]: Level A ¹¹

215 **Reconsideration Packet**: a method by which interested parties can request a complete or
216 partial revision to an active LCD. The reconsideration process is available for final LCDs only to
217 the fiscal intermediary (FI). Requests must identify the language that the requestor wants
218 added or deleted as well as include justification for the change supported by new evidence in
219 the medical literature. Legible hard copies of published evidence must be included.

220 **National and Local Coverage Determinations (NCD or LCD)**: A determination whether or not an
221 item or service is reasonable or necessary for a Medicare beneficiary. A NCD guidance
222 document provides broad guidelines for all Medicare beneficiaries, whereas the LCD is a
223 decision made by the fiscal intermediary or carrier under part A or part B for the location of the
224 patient is treated.

225 **Notice of Non Coverage (NONC):** a written notice given to a patient who is covered under a
226 commercial insurance plan before the patient receives a medication for an off-label indication
227 that has been denied for payment (e.g. unsuccessful predetermination), in which the patient
228 may be responsible for payment.

229 **Payer requirements:** guidelines for reimbursement decisions vary between payers.

230 i. **Commercial:** use clinical guidelines, pathways and policies; some defer to CMS
231 requirements (NCD, LCD, approved compendia, evidence from approved peer reviewed
232 journals)

233 ii. **Medicare vs Medicare Advantage:** original Medicare is governed by Local and
234 National Coverage Decisions (LCD and NCD), CMS approved compendia, and evidence
235 form CMS peer reviewed journals. For Managed Medicare refer to Commercial above.

236 iii. **Medicaid vs Managed Medicaid:** Medicaid is similar to original Medicare. Refer to
237 Commercial above for Managed Medicaid

238 iv. **VA:** Restricted formulary and clinical guidelines

239 **Peer-to-Peer Discussion:** a medical peer-to-peer review process occurs when an institution or
240 practice requests for a specific patient case to be reexamined following an adverse clinical
241 determination being made for that patient. This process allows the attending, treating or
242 ordering physician to provide additional information regarding the patient situation and further
243 discuss the case with the intent to override the initial adverse determination.

244 **Peer Reviewed Scientific Journal:** a journal that has submitted most of its published articles for
245 review by experts who are not part of the editorial staff. The numbers and kinds of manuscripts
246 sent for review, the number of reviewers, the reviewing procedures and the use made of the
247 reviewers' opinions may vary, and therefore each journal publicly discloses its policies in the
248 Instructions to Authors for the benefit of readers and potential authors.¹⁰

249 Publications recognized by the Center for Medicare and Medicaid Services:

250 American Journal of Medicine;

251 Annals of Internal Medicine;

252 Annals of Oncology;

253 Annals of Surgical Oncology;

254 Biology of Blood and Marrow Transplantation;

255 Blood;

256 Bone Marrow Transplantation;

257 British Journal of Cancer;

258 British Journal of Hematology;

259 British Medical Journal;

260 Cancer;

261 Clinical Cancer Research;

262 Drugs;

263 European Journal of Cancer (formerly the European Journal of Cancer and Clinical Oncology);

264 Gynecologic Oncology;

265 International Journal of Radiation, Oncology, Biology, and Physics;

266 The Journal of the American Medical Association;
267 Journal of Clinical Oncology;
268 Journal of the National Cancer Institute;
269 Journal of the National Comprehensive Cancer Network (NCCN);
270 Journal of Urology;
271 Lancet;
272 Lancet Oncology;
273 Leukemia;
274 The New England Journal of Medicine; or
275 Radiation Oncology

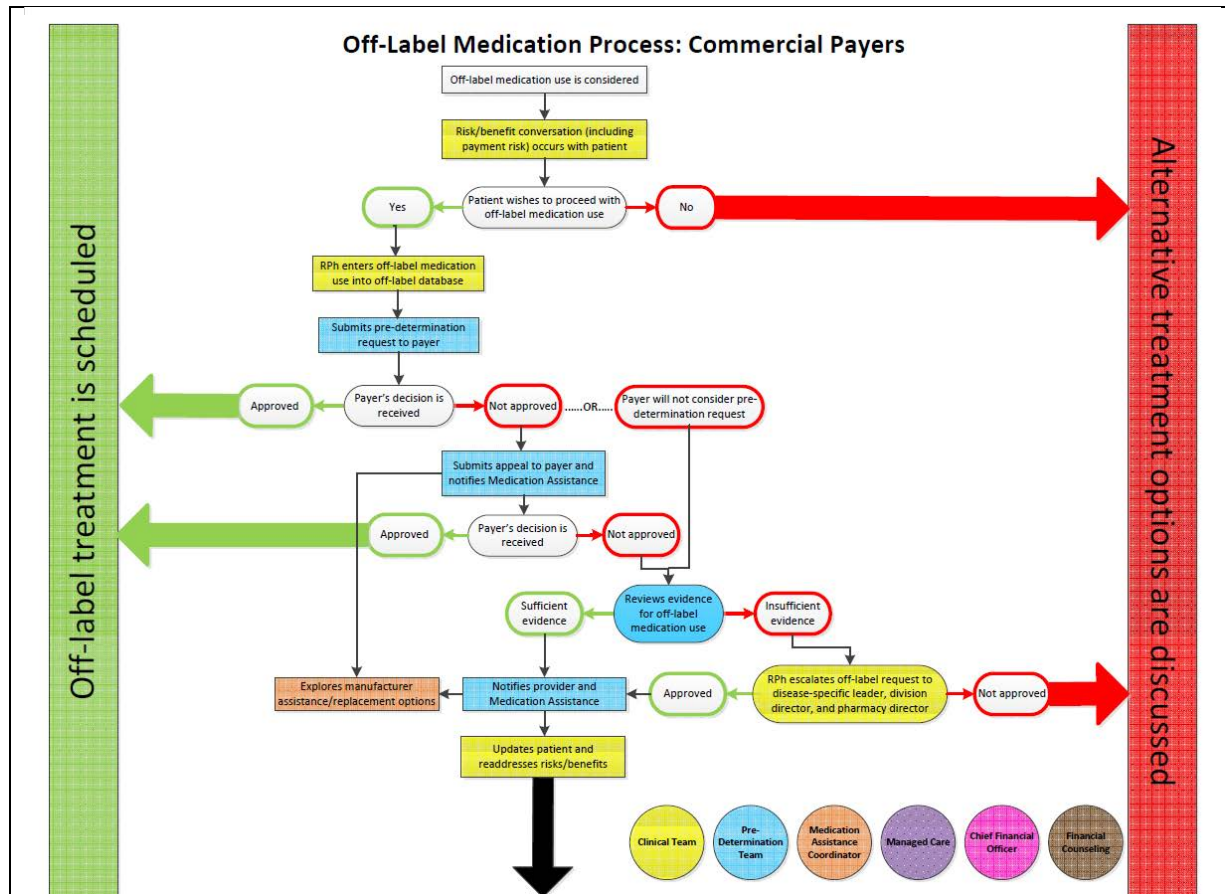
276 **Pharmacy benefit plan:** the level of health insurance coverage, which pays for prescription
277 drugs or medications. This can be provided through retail, specialty or mail order pharmacies.
278 In contrast to the medical benefit, this is the benefit typically pays for procedures, physician
279 visits, medication infusions and injection conducted in a physicians' office or infusion center.

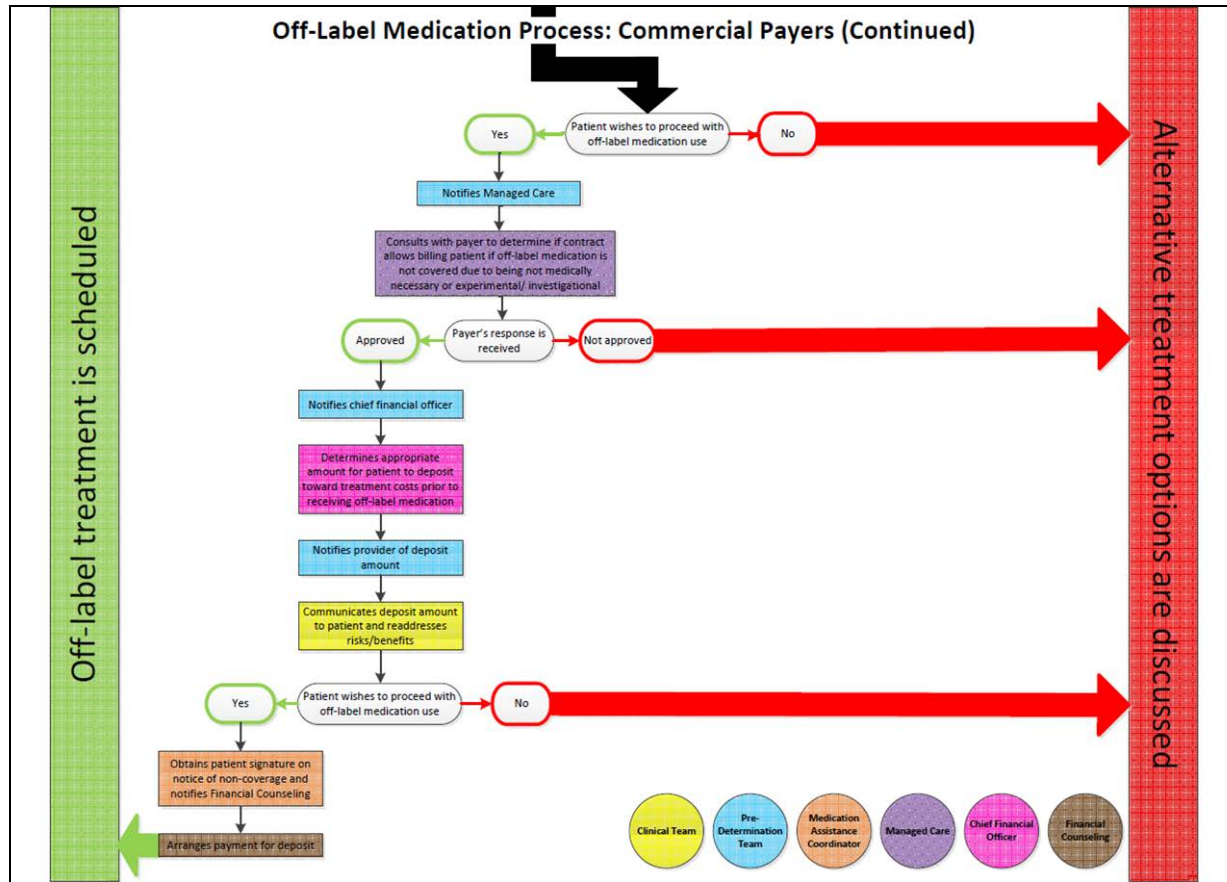
280 **Pre-determination:** A process whereby a submission to an insurance company initiates a
281 patient specific review of clinical information when a medication use is deemed off-label to
282 determine if it is to be considered medically necessary, not medically necessary, experimental
283 or investigational and not medically necessary. The insurance company reviews standard
284 medical practice, relevant peer reviewed scientific published data, physician and professional
285 society recommendations and other relevant clinical factors as they relate to the patient's
286 clinical circumstances.

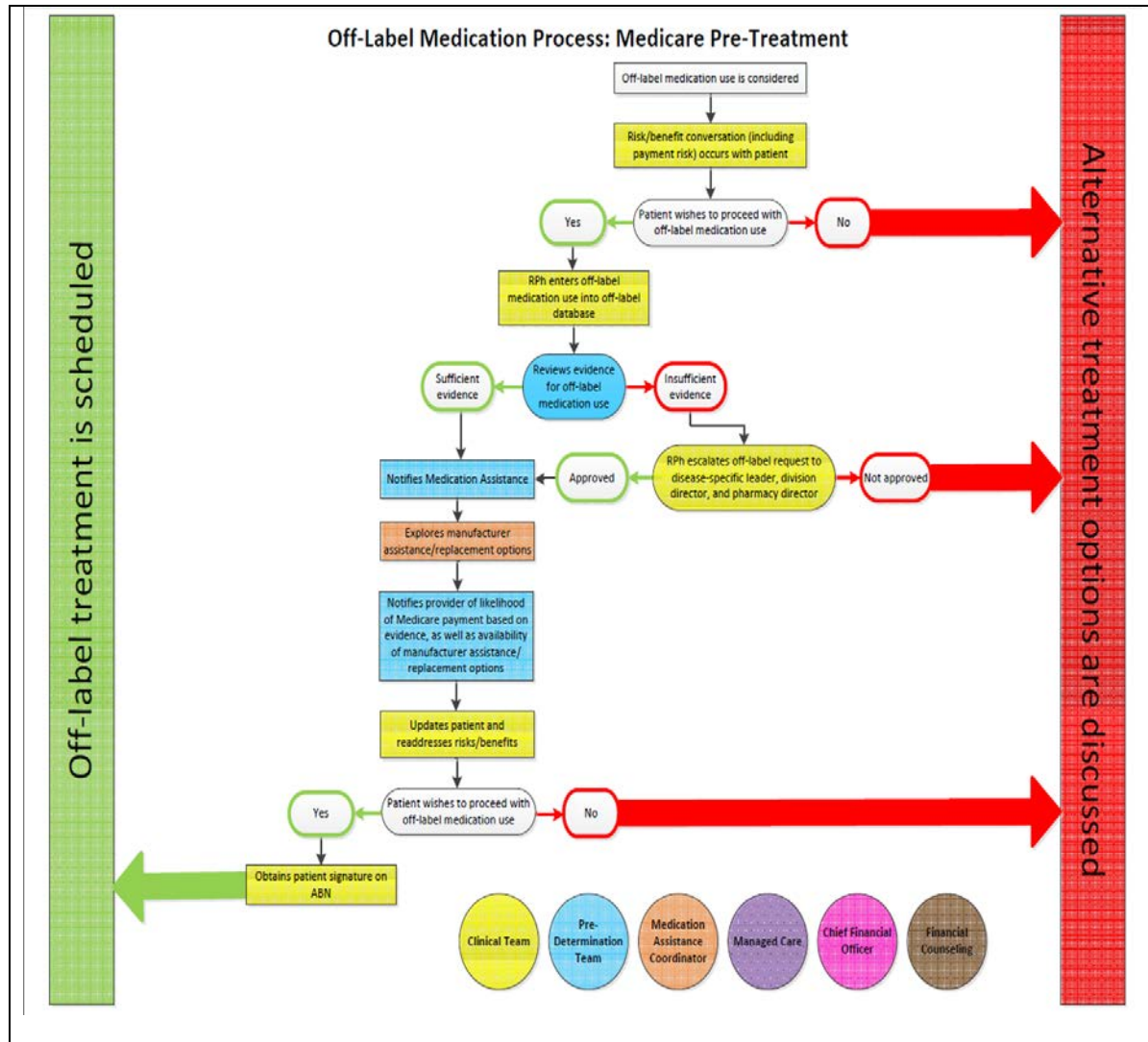
287 **Prior Authorization/Pre-Certification:** a requirement of the insurance company which includes
288 evaluation of the medical necessity, appropriateness and efficient use of health care services,
289 procedures and facilities under the provisions of the patient's health benefits plan.¹²

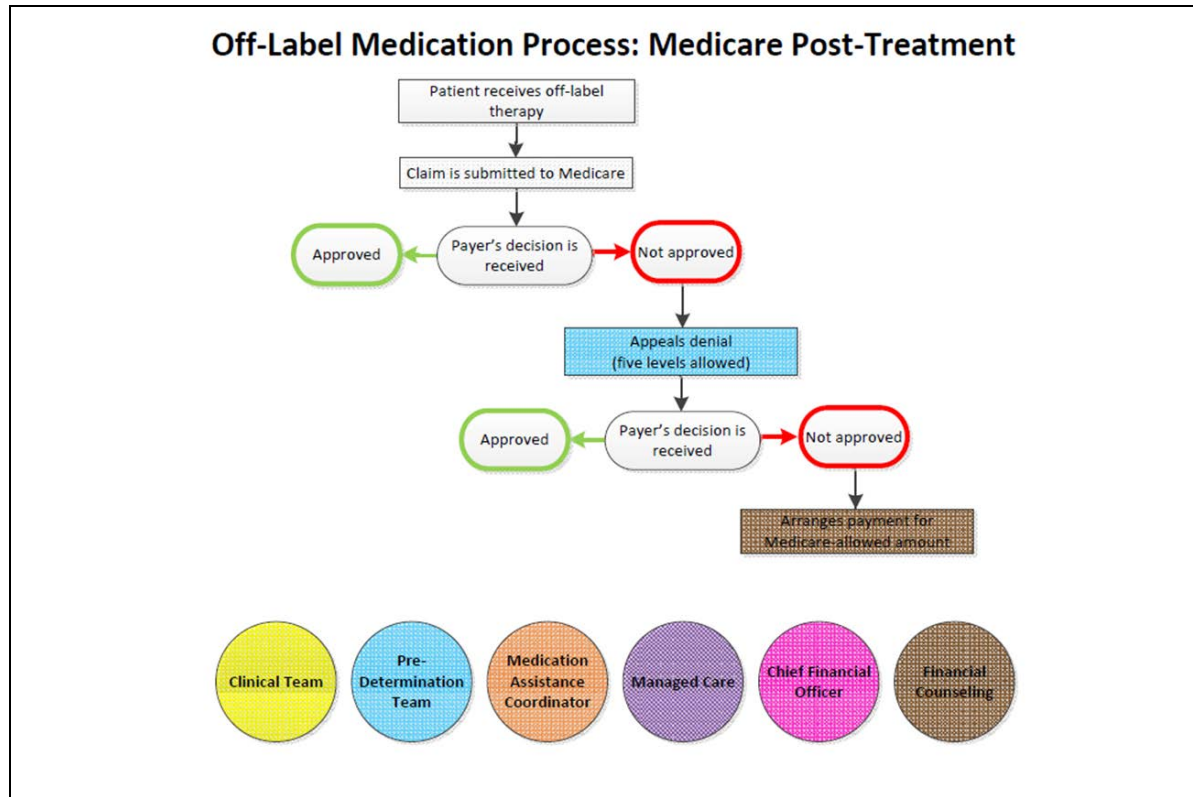
290 **Published Guidelines** (ASCO, NCCN, Chest, etc.): systematically developed statements to assist
291 practitioners and patient decisions about appropriate health care for specific circumstances
292 which may include reviews of research about the potential benefits and harms of alternative
293 drugs, devices, and other healthcare services in order to provide the best evidence to inform
294 clinical decisions. Trustworthy guidelines should be based on a systematic evidence review,
295 developed by panel of multidisciplinary experts, provide a clear explanation of the logical
296 relationships between alternative care options and health outcomes, and provide ratings of
297 both the quality of evidence and the strength of the recommendations.¹³

298 Appendix B









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