# Molina Clinical Policy
# Clinical Trials and Rare Disease: Policy No. 183

**Last Approval: 6/14/2023**
**Next Review Due By: June 2024**

## DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

## OVERVIEW

Clinical trials involve participants who receive specific interventions as detailed in a research plan or protocol. Investigators determine the safety and efficacy of specific outcomes related to an intervention – these may include medical products (e.g., drugs, devices, procedures) or behavior modification (e.g., diet). Trials may compare a new medical approach to an available standard approach, to a placebo containing no ingredients, or to no intervention. Other trials may compare existing, available interventions. While the Food and Drug Administration (FDA) does not conduct trials, they define phases of drug development trials and provide oversight for some trials involving human drugs, biological products, and devices. In addition, certain trials are required to be registered in the ClinicalTrials.gov database (National Library of Medicine, 2019).

The Patient Protection and Affordable Care Act (PPACA) requires the coverage of routine patient costs associated with approved clinical trials. Clinical trials should have the following characteristics (CMS, 2015):

- Determines if an intervention can improve health outcomes.
- It is heavily supported by scientific literature or will clarify health outcomes of common clinical interventions.
- It is not duplicative of existing studies.
- Design appropriately answers the research question.
- Sponsored by a reliable organization or individual.
- Complies with federal regulations related to the protection of human subjects.
- All parts are conducted aligning with the appropriate standards of scientific integrity.

## RELATED POLICIES

*MCP-184: Experimental and Investigational Services*
*MCP-332: Medically Necessary Services*

## COVERAGE POLICY

**This policy outlines recommendations for coverage of services and/or supplies for Molina Healthcare members enrolled in clinical trials.**

Coverage of Clinical Trials and/or related services and supplies may be mandated by applicable legal requirements of the State, Federal government or Centers for Medicare and Medicaid Services (CMS) for Medicare and Medicaid members. Additionally, some benefit plans may exclude coverage. **Please check State Health Plan regulations for all lines of business and local compliance and/or legal team before applying this policy.**

The requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

If there are no mandates or exclusions in the benefit plan, **coverage may be considered on a case-by-case basis** when **ALL** the following criteria and supporting documentation are met:

1. Member has a current *life-threatening, chronic, or **severely debilitating diagnosis (e.g., cancer, kidney failure, AIDS (acquired immunodeficiency syndrome), and serious rare diseases with an incidence of less than 1:200,000).

   ** A life-threatening condition means any disease or condition from which the likelihood of death is probable unless the course of the disease or condition is interrupted.*
   *** A debilitating condition is defined as the member being unable to engage in substantial gainful activities due to the medically determinable mental or physical condition; the impairment is expected to result in death and has remained or expected to remain continuously for at least a twelve-month period*

**AND**

2. Other treatment options are not available or have been exhausted. Standard therapies have either not been effective in significantly improving the member's condition or are not medically appropriate; **AND**

3. The trial must have therapeutic intent and not solely designed to test toxicity or disease pathophysiology; **AND**

4. The clinical trial is approved by all relevant institutional review boards and defined as an ***approved clinical trial** under the under Section 10103(c) of Patient Protection and Affordable Care Act of 2010 as a Phase I, Phase II, Phase III, or Phase IV clinical trial that is conducted in relation to the prevention, detection, or treatment of cancer or other life-threatening disease or condition and is **ONE** of the following:

   a. A federally funded or approved trial by **ONE** of the following agencies: National Institutes of Health (NIH); National Cancer Institute (NCI), Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, CMS; **OR**
   b. A cooperative group or center of any of the above listed entities or the Department of Defense (DoD) or Department of Veterans Affairs (VA); or
   c. A qualified nongovernmental research entity identified in the guidelines issued by the NIH for center support grants; or
   d. The Departments of VA, DoD, or Energy if the trial has been reviewed and approved through a system of peer review comparable to the system used by the NIH and that ensures unbiased review of the highest scientific standards by qualified individuals who have no interest in the outcome of the review; **OR**
   e. The study or investigation is conducted under an investigational new drug application reviewed by the FDA; **OR**
   f. The study or investigation is a drug trial that is exempt from having such an investigational new drug application.

**AND**

5. **ALL** the following are met by Member with documentation:
   a. All clinical trial protocol requirements are met for enrollment as a participant in the clinical trial; and
   b. Provide informed consent; and
   c. Members must be treated according to clinical trial protocol.

**AND**

6. Requested treatment must demonstrate a clinical benefit over current existing treatment options; **AND**

7. There is a reasonable expectation that the treatment will extend the member's life or considerably improve the member's physical and/or social functioning, thereby improving the member's capacity to perform relevant daily activities.

## Routine Costs During Clinical Trials
**(CMS, 2015 & 2007)**

Covered routine patient care costs for an enrolled member in an approved clinical trial requested include:

1. Items or services that are typically provided absent a clinical trial (e.g., conventional care, laboratory services, radiologic services, office visits, hospital services, etc.).
2. Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications.
3. Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service, in particular for the diagnosis or treatment of complications.

*Reference: CMS NCD Routine Costs in Clinical Trials (310.1)*

## Limitations and Exclusions

**(CMS, 2015 & 2007)**

The following limitations/exclusions apply to routine costs and services from participation in a qualifying clinical trial for Molina members that meet the clinical coverage criteria (as outlined above). Routine patient costs NOT eligible for coverage include:

1. Clinical trials that do not meet the criteria in the 'Coverage Policy' section above (e.g., Phase 0 drug Clinical Trials, a patient registry).
2. The experimental intervention itself (except medically necessary Category B investigational devices).
3. Items and services customarily provided by the research sponsors free-of-charge for any enrollee in the trial.
4. Items and services necessary solely to satisfy data collection needs of the clinical trial (e.g., "protocol-induced costs").
5. Routine patient costs obtained out-of-network where non-network benefits do not exist under the plan (NOTE: All applicable plan limitations for coverage of out-of-network care will apply to routine patient care costs in clinical trials).
6. Travel and transportation expenses, including but are not limited to:
   - Any transportation costs to and from trial location (e.g., personal vehicle mileage reimbursement, taxi, medical van, ambulance, commercial airline, train, rental car expenses).
   - Lodging and meals.
7. Non-FDA authorized interventions or medications delivered or made available to a member during a covered clinical trial will not be covered after the trial is completed.

## Medicare Members

- Coverage for items and services that may be covered or the regulations on Category B exemptions for investigational devices are found in 42 CFR 405.201-405.215, 411.15, and 411.406.
- The Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.

**DOCUMENTATION REQUIREMENTS.** Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

# SUMMARY OF MEDICAL EVIDENCE

## Diversity in Clinical Trials

Turner et al. (2022) analyzed clinical trial records from all trials registered in ClinicalTrials.gov between March 2000 to March 2020. Previous analysis has been limited due to small cohorts and a lack of data related to one's race and/or ethnicity. Using a Wilcoxon test, minority participation was compared to 2010 United States Census data. A total of 20,692 trials based in the United States were included which represented 4 million enrollees. A total of 43% (8,871) of trials reported race/ethnicity data. The highest number of enrollees were White (80%) followed by Black (10%), Hispanic/Latino (6%), Asian (1%), and American Indian (<1%). Schwartz et al. (2023) highlight the importance of

participation of racial and ethnic groups. The National Academies of Sciences, Engineering, and Medicine (NASEM) provided suggestions including earning and building trust, promoting fairness, and generating biomedical knowledge. The NASEM report notes that reducing barriers may include mobile recruitment strategies, providing transportation or parking vouchers, and offering fair compensation and incentives to minimize gaps in representation. In addition, the report described the importance of building inclusive trial infrastructure in communities that are underserved.

**National and Specialty Organizations**

The **American Society of Clinical Oncology (ASCO)** Health Disparities Committee published a policy statement on *Cancer Disparities and Health* Equity (2020). Several recommendations were made to achieve health equity:

- Ensure Equitable Access to High-Quality Care
- Ensure Equitable Access to Research
- Address Structural Barriers

The ASCO also published a position statement on *Strategies for Reducing Cancer Health Disparities Among Sexual and Gender Minority Populations* (Griggs et al., 2017). The ASCO recommendations include promotion and inclusion of sexual and gender minority (SGM) status as a required data element in cancer registries and clinical trials. While data are now collected from federally funded health surveys (e.g., National Health and Nutrition Examination Survey, the National Health Interview Survey, and the Behavioral Risk Factor Surveillance System), data are not routinely collected in other clinical trials, surveys, or epidemiologic studies. This omission slows research among SGM populations – the ASCO states that efforts should be made to standardize collection of the data including training staff on how to be sensitive and respectful when collecting information from individuals.

## SUPPLEMENTAL INFORMATION

**Definitions**

**Category B (Non-Experimental / Investigational) Device** refers to a device for which the incremental risk is the primary risk in question (that is, initial questions of safety and effectiveness of that device type have been resolved), or it is known that the device type can be safe and effective because, for example, other manufacturers have obtained FDA premarket approval or clearance for that device type.

**Clinical Trial/Studies involving Investigational New Drugs** (FDA, 2018)

- **Phase I** trials are concerned primarily with determining dosing, documenting how a drug is metabolized and excreted and identifying acute side effects. A small number of healthy volunteers (between 20 and 80) are evaluated in Phase I trials.
- **Phase II** trials involve approximately 100 to 300 participants who have a disease or condition that the product could treat. Researchers seek to gather further safety data and preliminary evidence of the drug's efficacy, and they develop and refine research methods for future trials. Drugs showing effectiveness with little risks identified will move to Phase III.
- **Phase III** trials include a population of patients between 1,000 to 3,000 with a disease. This phase further tests the product's effectiveness, monitors side effects, and compares the product's effects to a standard treatment, when available.
- **Phase IV** trials are conducted after a product is already approved and, on the market, to identify potential long-term risks, benefits, and optimal use, or to test the product in different populations of people, such as pediatric populations.

Clinical trial phases for **cancer** are defined by the NCI are as follows:

- **Phase I** studies are the initial clinical tests for new treatments to define a safe dose and schedule of agent or combination of agents or to evaluate the feasibility of combining treatment modalities in typically less than 100 patients. This phase develops because of promising pre-clinical data, such as in vitro cytotoxicity in tumor cell lines and safe administration with reproducible antitumor effect in animals if a stable and safe formulation of the agent is available.
- **Phase II** studies assess the antitumor efficacy of a new cancer agent, a new combination of agents, a new modality of therapy and further determination of toxicity. The new treatment is given to groups of patients with

one type of cancer or related cancers using the dosage and scheduling found safe from Phase I trials. Unusual or chronic toxicities may appear during Phase II testing; this is considered when deciding whether the agent should be further evaluated in Phase III studies.

- **Phase III** studies are designed to compare one or more treatments. A new drug or drug combination may be tested against one of proven efficacy. Phase III studies often have multiple endpoints. Overall and disease-free survival is nearly always endpoints; differences in response rates, toxicity, patterns of recurrence, and quality of life might also be endpoints. The new drug or drug combination will be found to be inferior, equivalent, or superior to the standard treatment in respect to the major endpoints. The degree of difference will be known, and statistical significance will be estimated.
- **Phase IV** trials are conducted to further evaluate the long-term safety and effectiveness of a treatment. They usually take place after the treatment has been approved for standard use. Several hundred to several thousand people may take part in a phase IV study.

**Rare Disease.** A condition will be considered a rare disease when a review of the current published peer reviewed medical literature, the NCI Physician Data Query (PDQ), the National Comprehensive Cancer Network Guidelines, and other appropriate sources indicates that there is no standard treatment available for the condition. The Genetic and Rare Disease Information Center offers a database of rare diseases.

National Center for Advancing Translational Sciences Genetic and Rare Disease Information Center. Main page. Accessed April 24, 2023. http://rarediseases.info.nih.gov/.

## CODING & BILLING INFORMATION

| Modifier | Description |
|---|---|
| *Coding Clarification: These modifiers are not required for Clinical Trial claims; nonetheless, if one of these modifiers is present, the claim is deemed a Clinical Trials claim.* | |
| **Modifier Q0** | Investigational clinical service provided in a clinical research study that is in an approved clinical research study |
| **Modifier Q1** | Routine clinical service provided in a clinical research study that is in an approved clinical research study |

**HCPCS (Healthcare Common Procedure Coding System) Codes**

| HCPCS | Description |
|---|---|
| **S9988** | Services provided as part of a Phase I clinical trial |
| **S9990** | Services provided as part of a Phase II clinical trial |
| **S9991** | Services provided as part of a Phase III clinical trial |
| **G0294** | Noncovered procedure(s) using either no anesthesia or local anesthesia only, in a Medicare qualifying clinical trial, per day |
| **G0293** | Noncovered surgical procedure(s) using conscious sedation, regional, general, or spinal anesthesia in a Medicare qualifying clinical trial, per day |

| **HCPCS codes not covered for indications listed (not all inclusive):** | |
|---|---|
| **S9992** | Transportation costs to and from trial location and local transportation costs (e.g., fares for taxicab or bus) for clinical trial participant and one caregiver/companion |
| **S9994** | Lodging costs (e.g., hotel charges) for clinical trial participant and one caregiver/companion |
| **S9996** | Meals for clinical trial participant and one caregiver/companion |

**CODING DISCLAIMER.** Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

## APPROVAL HISTORY

| | |
|---|---|
| **6/14/2023** | Policy reviewed, updated Overview section and summary of medical evidence. Initial overview section very limited. Also included diversity in clinical trials in summary of evidence. No changes to criteria. Coding updated to include G0293-4. |
| **6/8/2022** | Policy revised. Added 'Related Polices' section. Rewrote 'Coverage Policy' section. Notable revisions include:<br>• Clarified 'a life-threatening condition' in criterion #1.<br>• Removal criteria requiring two (2) independent scientific or medical documents.<br>• Removal of the procedure section for internal process (at the end of the coverage criteria section previously).<br>• Added criterion "The trial must have therapeutic intent and not solely designed to test toxicity or disease pathophysiology."<br>• Added a criterion defining a qualifying clinical trial.<br>• Added the 'Routine Cost during Clinical Trials' section and a 'Limitations/Exclusions' section.<br>• Added notation for Medicare members (at the end of the coverage criteria section).<br>• Added definition for Category B devices in supplemental information section.<br>• Updated coding section. |
| **6/17/2020** | Policy reviewed, no changes. |
| **6/9/2021** | Policy reviewed, no changes. |
| **6/19/2019** | Policy reviewed, changed the word technology to treatment for clarification on page 2, policy statement. |
| **7/10/2018** | Policy reviewed, no changes. |
| **6/22/2017** | Policy reviewed, no changes. |
| **6/15/2016** | Policy reviewed, no changes. |
| **12/16/2015** | Policy reviewed, no changes. |
| **6/25/2014** | New policy. |

## REFERENCES

1. Centers for Medicare and Medicaid (CMS). Local coverage article: Clinical trials – medical policy article (A52840). Effective Date October 1, 2015. Accessed April 20, 2023. https://www.cms.gov/.
2. Centers for Medicare and Medicaid (CMS). National coverage determination (Routine costs in clinical trials (publication section 310.1, publication 100-3). Effective July 9, 2007. Accessed April 20, 2023. https://www.cms.gov/.
3. Genetic and Rare Disease Information Center. Main page. Published (date unknown). Accessed April 24, 2023. http://rarediseases.info.nih.gov/.
4. Griggs J, Maingi S, Blinder V, et al. American Society of Clinical Oncology position statement: Strategies for reducing cancer health disparities among sexual and gender minority populations. J Clin Oncol. 2017 Jul 1;35(19):2203-2208. doi: 10.1200/JCO.2016.72.0441. PMID: 28368670.
5. National Library of Medicine. Learn about clinical studies. Updated March 2019. Accessed April 24, 2023. http://www.clinicaltrials.gov.
6. Patel MI, Lopez AM, Blackstock W, et al. Cancer disparities and health equity: A policy statement from the American Society of Clinical Oncology. J Clin Oncol. 2020 Oct 10;38(29):3439-3448. doi: 10.1200/JCO.20.00642. PMID: 32783672. PMCID: PMC7527158.
7. Schwartz AL, Alsan M, Morris AA, et al. Why diverse clinical trial participation matters. N Engl J Med. 2023 Apr 6;388(14):1252-1254. doi: 10.1056/NEJMp2215609. PMID: 37017480.
8. Turner BE, Steinberg JR, Weeks BT, et al. Race/ethnicity reporting and representation in US clinical trials: A cohort study. Lancet Reg Health Am. 2022 Jul;11:100252. doi: 10.1016/j.lana.2022.100252. PMID: 35875251. PMCID: PMC9302767.
9. United States Department of Health and Human Services (HHS). Medicare benefit policy manual – chapter 14, section 20. Guidance for Food and Drug Administration (FDA)-approved Investigational Device Exemption (IDE) studies. Published January 1, 2020. Accessed April 20, 2023. https://www.hhs.gov/guidance/document/medicare-benefit-policy-manual-chapter-14-medical-devices.
10. United States Department of Health and Human Services (HHS). Patient Protection and Affordable Care Act and Health-Related Portions of the Health Care and Education Reconciliation Act Of 2010. 42 U.S.C. § 18001 et seq. (2010). Accessed April 30, 2023. https://www.hhs.gov/sites/default/files/ppacacon.pdf?languages.
11. United States Food and Drug Administration (FDA). Step 3: Clinical research. Published January 4, 2018. Accessed April 20, 2023. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research.

## APPENDIX

***Reserved for State specific information.*** *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*