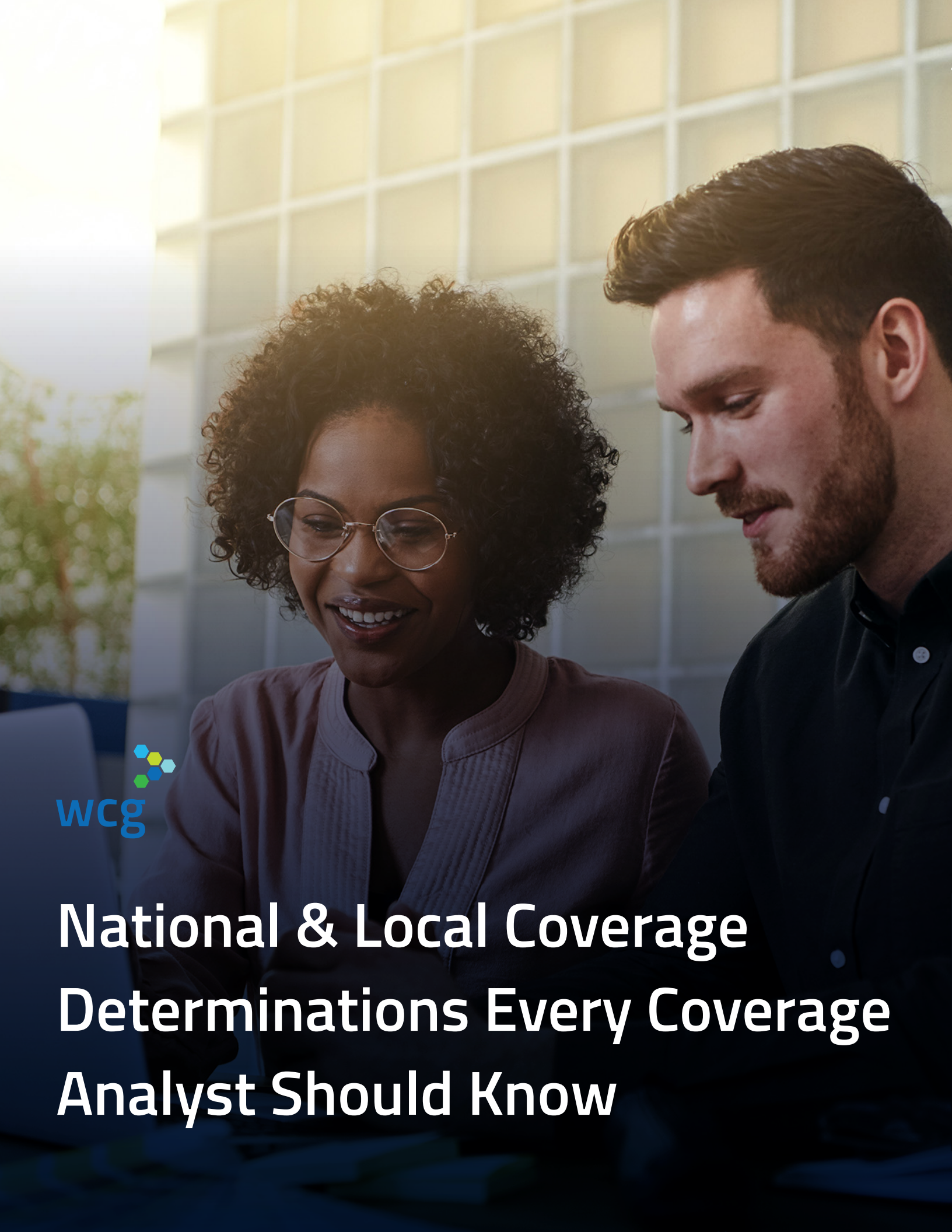

National & Local Coverage Determinations Every Coverage Analyst Should Know

Requirements for Medicare Coverage

For a clinical trial to qualify for Medicare coverage under entity 310.1:

- The study needs to be under a Medicare benefit category, such as Drugs and Biologics.
- The trial must have therapeutic intent.
- Patients enrolling must be diagnosed with a disease, such as COVID-19 or breast cancer.
- The study must be deemed, meeting one of these criteria: funded by a government agency, supported or in collaboration with one of the approved government groups, conducted under an Investigational New Drug (IND) application or IND exempt.

What does it mean when a clinical trial qualifies for Medicare coverage under NCD 310.1? Medicare has defined the following items as routine costs in a clinical trial and covered by Medicare:

- Routine items or services performed absent a clinical trial. For example, if a patient population is diagnosed with breast cancer, these patients will undergo routine care for breast cancer irrespective if they participate in a clinical. During coverage analysis, look at national treatment guidelines or appropriate use imaging criteria to evaluate if items are billable to Medicare in the routine care setting.
- Coverage for items or services required for the provision of an investigational product - this may include an IV infusion or a subcutaneous injection of the drug itself.
- Items or services used to prevent, detect, monitor or treat the side effects of a study regimen - to identify side effects, look at the informed consent or investigator's brochure, as well as drug labels for treatments available on the market today.

Note that Medicare will never pay for items provided for free – or otherwise paid for – by the sponsor.

CASE STUDY #1
COVID-19

Let's consider how NCD 310.1 will aid with coverage analysis of a clinical trial studying the effectiveness of drug ABC123 in decreasing symptoms of COVID-19 on hospitalized patients. The trial is conducted under an IND. The sponsor is not paying for daily physical exams or CMPs during the hospitalization or at screening, and the sponsor is not paying for the IV infusion of ABC123.

- Is this study considered a qualifying clinical trial under NCD 310.1?
- This study would fall under the benefit

category of drugs and biologics, enrolling patients diagnosed with COVID-19. The study is conducted under an IND, so this is a qualifying clinical trial under NCD 310.1.

- What about Medicare coverage of the physicals and CMPs for which the sponsor is not paying? National guidelines for the treatment of hospitalized COVID-19 patients include a recommendation to perform a physical exam and a CMP when the patient is first admitted to the hospital and every day that they are hospitalized for COVID-19. Since the physical exam and lab tests would be billed to the patient's insurance, regardless of if they are enrolled in this clinical trial or not, these items are considered routine care. They would be billable to Medicare, supported by NCD 310.1.
- What about the IV infusion of ABC123? Remember, NCD 310.1 includes coverage for items or services required for the provision of the investigational product. Since we need to perform an IV infusion to administer ABC123, Medicare sees this infusion as a required item to provide the study drug, so it is billable under NCD 310.1.

NCD 310.1 includes a small but significant statement for coverage analysis: All other Medicare rules apply. What does that mean? Well, NCD 310.1 is not the only Medicare NCD that clarifies coverage for items or services such as lab tests and MRIs – other NCDs exist, and will impact a coverage analysis. Similarly, LCDs will provide coverage guidance for items or services, which will apply to a specific region of the country. Additionally, the Medicare Benefit Policy Manual and the Medicare Claims Processing Manual delve into how many items are or are not billable under Medicare rules. Therefore, an analyst needs to determine how NCDs, LCDs and Medicare Manuals are involved to perform a complete coverage analysis. We'll take a closer look at how these other sources can impact an analysis, below:

CASE STUDY #2
METASTATIC COLON CANCER

This case study involves patients with metastatic colon cancer. To determine LCDs, we know that the institution is in Florida. This trial is qualifying, and none of the items are being paid for by the sponsor. Required imaging is standard for oncology studies: a CT scan of the chest, abdomen, pelvis and brain before treatment, and then every two cycles throughout treatment. The protocol also requires magnesium and GGT testing once per cycle throughout treatment. Can this institution bill these tests and scans to Medicare?

- NCD 220.1 states that diagnostic examinations of the head and other parts of the body performed by CT scanners are covered if medical and scientific literature plus opinion support the effective use of a scan. The oncology imaging appropriate use criteria (AUC) recommends for

metastatic colon cancer, including CT scans of the chest, abdomen and pelvis at pre-therapy and for monitoring of therapy.

- How do we interpret this information? NCD 220.1 leads us back to the medical literature required to determine whether an item is performed absent to trial per NCD 310.1. Since the NCCN AUC supports the CT scans, this meets the definition of a routine cost under both NCD 310.1 and NCD 220.1 requirements. On the other hand, a CT scan of the brain is not included in this appropriate use criteria, so we cannot consider the cost routine.
- Magnesium is not indicated as a recommendation in the colon cancer guidelines. Still, the study drug's labeling information states that it is known to cause an increase in magnesium levels. LCD L34014, the Florida LCD for magnesium testing, states that magnesium testing will be considered medically necessary in the presence of signs or symptoms of hypomagnesemia or hypermagnesemia.
- How do we interpret this information? NCD 310.1 supports coverage for the prevention and monitoring of potential study drug complications. Since the study drug is known to cause magnesium-related side effects, a magnesium test once per cycle could be billed to prevent and monitor potential complications per NCD 310.1. However, LCD L34014 requires that the patients have existing signs or symptoms of abnormal magnesium levels to justify this coverage. Even though coverage is supported under NCD 310.1, if these LCD conditions are not met, the magnesium test cannot be billed to Medicare.
- Similarly, GGT testing is not included in colon cancer guidelines. Labeling information for the study drug states that it is known to cause increased liver enzymes but does not specifically recommend GGT testing. GGT falls under NCD 190.32, which states that it is indicated to provide information about known or suspected hepatobiliary disease, e.g., when using medications known to have a potential for causing liver toxicity. However, it is generally unnecessary to repeat a GGT after a normal result unless new indications are present.
- How do we interpret this information? NCD 310.1 supports billing for the prevention and monitoring of potential studies or complications. The study drug in this case study is known to cause liver-related side effects. Per NCD 310.1, GGT testing once per cycle could be billed to prevent and monitor these potential complications. The NCD specifically limits drug side effect monitoring as an indication for coverage, but per the manufacturer's recommendation, the drug label for the study does not actually mention monitoring GGT.
- The NCD also requires a new indication to be present for repeat testing after a test result. We cannot predetermine if every

patient enrolling will have an abnormal or normal test result at each cycle visit for this study. Therefore, we conclude that GGT cannot be billed to Medicare.

CASE STUDY #3
AUTOLOGOUS CAR-T CELL THERAPY

This study focuses on patients having diffuse large B-cell lymphoma (DLBCL). It is a qualifying clinical trial under NCD 310.1 to study the effects of autologous CAR-T cell therapy on the patient's lymphoma. This study is performed in a Pennsylvania research site. We will focus on Medicare coverage for the protocol required items: leukapheresis (harvesting patient blood cells to manufacture the CAR-T cell product), infusion of the CAR-T cell product, hepatitis B testing, a CBC at screening and every day during the inpatient hospitalization following the CAR-T cell infusion, and finally, ferritin testing three times per week during the first week of post-infusion hospitalization.

- Medicare has released a new NCD 110.24 specifically for CAR-T cell therapy. Medicare will cover the use of CAR-T cell therapy in a clinical trial if the study uses the patient's own engineered T cells, and that the clinical trial qualifies for coverage under NCD 310.1. What exactly does this NCD cover? NCD 110.24, together with the Medicare Benefit Claims Processing Manual, provides coverage for leukapheresis. In addition, NCD 110.24 covers the preparation of the cells for transport, receipt and preparation of the cells at the research site, plus administration of the CAR-T cells to the patient. In this case study, both the leukapheresis and the administration of the CAR-T cell product are covered under NCD 310.1 and NCD 110.24.
- What about lab tests? National guidelines recommend hepatitis B testing for all patients with DLBCL, so this test is routine care under NCD 310.1. However, "all other Medicare rules apply." NCD 210.6 states that the patient must be at "high risk" for hepatitis B to receive coverage for this test; and, being immunocompromised or having cancer is not defined as high risk for this NCD. Additionally, the NCD states that this test must be ordered in the primary care setting. Since our research site cannot guarantee that every patient screened will be at "high risk" for hepatitis B at screening, and those screening procedures are not performed at the primary care setting, this test is not billable to Medicare, with coverage limited by NCD 210.6.
- What about CBC tests?
    - At Screening: NCD 190.15 generally supports coverage for patients with blood cell disorders and bone marrow dysfunction based on their lymphoma diagnosis. Additionally, per the national guidelines, this test is a routine cost for

patients with lymphoma. Our patient population is eligible for coverage for a CBC per NCD 190.15; so, the screening CBC is billable with coverage supported by NCD 310.1 and NCD 190.15.

- During the hospitalization after CAR-T cell infusion: The guidelines do not provide specific guidance on CBC testing frequency during inpatient hospitalization. Your site needs to determine a reasonable and necessary frequency for CBC testing for a hospitalized patient who recently received CAR-T cell therapy.

- Ferritin tests after treatment: This protocol requires three tests of ferritin in the first week of hospitalization following the CAR-T cell infusion. National guidelines state to test ferritin three times during the first few weeks following infusion, so we can use NCD 310.1 and the new NCD 110.24 by extension to cover the ferritin test. However, "all other Medicare rules apply." Ferritin is a laboratory test with an NCD that requires review. Medicare will pay for ferritin testing if that test is used to diagnose and manage iron overload or deficiency or inform or alter the patient's treatment. DLBCL is not associated with iron imbalances per the NCD; and, as this test is occurring post-infusion of the CAR T-cell therapy, the test will not inform or alter the patient's "treatment" at the time of testing. Additionally, NCD 190.18 states that Medicare will not cover "repeat" ferritin tests once a normal result has been established; and, we cannot guarantee at the time of coverage analysis that all patients in the study will have an abnormal ferritin result at the protocol required testing frequency. Therefore, this test is considered research related and non-billable, with coverage limited by NCD 190.18.

Note: You may recall that this case study took place in Pennsylvania; but we have not mentioned any LCDs. For this case study, there are no LCDs available in Pennsylvania for analysis. Remember to double check for LCDs for all items and services required in the clinical trial – these location-specific coverage determinations are important to reference and incorporate whenever they're applicable.

CASE STUDY #4
CONGESTIVE HEART FAILURE

Patients in this case study have congestive heart failure, and the institution is in California. This trial is qualifying, and no items are sponsor paid. The protocol requires that lipids and BNP be tested before treatment and then monthly during treatment. PT/INR testing must be performed every three weeks for patients taking warfarin. We will use NCD 310.1 and other applicable NCDs or LCDs to determine if this can be billed to the institution.

- The study drug is known to cause lipid-

related side effects. Lipid testing falls under NCD 190.23, stating that Medicare does not cover routine screening and prophylactic testing for lipid disorders. Lipid testing in this study is used to prevent and detect study product side effects, supported under NCD 310.1, but NCD 190.23 states that lipid testing is not indicated in asymptomatic individuals. Therefore, lipid testing in this trial is not covered by Medicare.

- Heart failure guidelines recommend BNP testing prior to treatment and indicate that BNP may help guide treatment for a patient. The California LCD for BNP testing states that BNP measurements for monitoring and managing congestive heart failure are non-covered. Guidelines support the test for the study's patient population, so this is supported under NCD 310.1. However, the LCD does not provide support for patients with congestive heart care, so this test cannot be billed to Medicare.
- The study drug has a bleeding side effect, and the protocol states that PT/INR is only required for patients who are taking warfarin. NCD 190.17 states that a PT may be used to assess patients taking warfarin, so this item can be billed.

CONCLUSION

Our case studies show that relying purely on NCD 310.1 alone can put sites at risk for improper billing. Determine which NCDs and LCDs impact coverage analysis at your site and build these into your CA templates and training documentation to save headaches down the road. Not all NCDs and LCDs limit coverage; some fill in the gaps when guidelines have limited or no details. Finally, some sponsors may expect certain items to be SOC based on guidelines, study product risks and the patient's underlying condition; they may not even consider NCDs or LCDs. Be prepared for negotiations.

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