Updates May 2021:
Updated EUA eligibility criteria for Eli Lilly & Regeneron
CMS payment changes for administration

Federal Response to COVID-19:
Monoclonal Antibody Playbook

Outpatient administration playbook for healthcare leadership

24 MAY 2021
Introduction

Comprehensive checklist overview

Activity 1: Define facilities and patient visit logistics
- Site will need dedicated outpatient COVID-19 treatment space
- Alternate site of care allowances and needs
- Manage patient flow in accordance with CDC guidelines
- Pharmacy Needs
- Testing Needs
- High level guidance on product shipping and storage

Activity 2: Ensure sufficient supplies
- Site supplies needed: Standard infusion supplies are required

Activity 3: Develop plan for staffing and personnel
- Treating patients needs support of healthcare providers, pharmacist, and nurses

Activity 4: Review drug administration process
- Multiple treatment pathways for symptomatic COVID-19 patients to receive care

Activity 5: Prepare for reimbursement and drug ordering
- Reimbursement process for mAbs therapeutic under Emergency Use Authorization (EUA)

Activity 6: Reporting process
- Reporting Needs
Introduction
This playbook is intended to support sites interested in administering COVID-19 monoclonal antibody (mAb) treatment under EUA including but not limited to:

- Existing hospital or community-based infusion centers
- Existing clinical space (e.g. urgent care, emergency depts)
- Ad hoc new infusion sites (e.g. "hospitals without walls")
- Long-term care facilities
- Home infusions

This playbook continues to evolve as other treatments and administration methods become available. We hope this playbook will be used to help healthcare facilities implement monoclonal antibody treatment in an outpatient setting for those with COVID-19.
Context of mAbs outpatient administration playbook

Proven operationally challenging to run monoclonal antibodies clinical trials in outpatient setting for variety of reasons

Initial EUAs were granted for Eli Lilly and Regeneron products in November 2020 only for outpatient setting

Expanded eligibility criteria for administration of both Eli Lilly and Regeneron products were released in May 2021 for outpatient setting

Monoclonal antibody infusion has been successfully implemented in a variety of outpatient settings

Scope of this playbook

Goal of playbook to articulate what is needed for outpatient administration at potential infusion sites:

- Supplies likely required for administration and potential challenges in procurement
- Personnel needed for infusions
- Space and logistics needed to safely treat COVID-19 patients and protect others
- Drug administration process
- Reimbursement process
- Reporting process
Monoclonal antibodies (mAbs) directly neutralize the COVID-19 virus and are intended to **prevent progression of disease**

mAbs are most effective when **given early in infection**

Product delivered via **single administration** (e.g., IV infusion)

**Evolving evidence** demonstrates promise of mAb products in outpatient settings

- Evidence from Eli Lilly mAb cocktail **showed potential to reduce hospitalization and death** in infected people if given early in infection (Phase 3 data of BLAZE-1 clinical trial)
- Phase 1 and 2 data from Regeneron mAb cocktail trial showed potential to decrease **viral load** and **reduced medical visits** in infected people if given early (Outpatient 2067 clinical trial)
mAbs products now available under EUA therefore...

Administration site **does not need to be a clinical trial site** to administer product

**Informed consent is not needed** to administer products under EUA

**No clinical data reporting required** beyond established mechanisms for tracking and reporting serious adverse events

**TeleTracking data reporting required** on utilization of product
Treatment eligibility

Products granted EUA for **mild to moderate COVID-19 cases** early in infection, who are at **high risk for progressing to severe COVID-19 and/or hospitalization**; with following criteria:

- Adult or pediatric (≥ 12 years of age and weighing at least 40kg) patient
- Confirmation via **positive PCR or antigen test**
- Treatment **as soon as possible** following positive viral test and **within 10 days of symptom onset**
- Patient symptomatic but **not yet progressed to require hospitalization or oxygen therapy (or increase from baseline home oxygen therapy)**

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and **authorization of mAb therapy is not limited to the medical conditions or factors listed above**. For **additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19**, visit the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

**HIGH RISK FACTORS INCLUDE, BUT ARE NOT LIMITED TO:**

- Older age (for example ≥ 65 years of age)
- Obesity or being overweight (for example, adults with BMI ≥ 25, or if age 12-17, have BMI ≥ 85th percentile for their age and gender based on CDC growth charts)
- Pregnancy
- Chronic Kidney Disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital abnormalities)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19 infection))
Monoclonal antibodies are under evaluation for additional indications.

Participation encouraged in clinical trials to assess additional drugs and indications.

Clinical trial information available at https://www.combatcovid.hhs.gov


Regeneron clinical trials: https://www.regeneron.com/covid19
EUA summary: REGEN-COV (casirivimab/imdevimab) (Regeneron)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products casirivimab/imdevimab to be administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Casirivimab/imdevimab are not authorized for use in patients:
- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity

Benefit of treatment with casirivimab/imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab/imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Casirivimab/imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

For additional information—please reference EUA factsheet and RegeneronEUA.com

Key caveats

The EUA is for the use of the unapproved products casirivimab/imdevimab to treat COVID-19.

Casirivimab/imdevimab are investigational drugs that have not been approved by the FDA for any use; and should not be considered the standard of care for treatment of patients with COVID-19.

It is not yet known if casirivimab/imdevimab are safe and effective for the treatment of COVID-19.

This use is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use, unless the authorization is terminated or revoked sooner.

Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS related to casirivimab/imdevimab.
EUA summary: bamlanivimab/ etesevimab (Eli Lilly)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab/ etesevimab to be administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization

Bamlanivimab/etesevimab are not authorized for use in patients:
- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity

Benefit of treatment with bamlanivimab/etesevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab/ etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation

Bamlanivimab/etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary

For additional information— please reference EUA factsheet

Key caveats

The EUA is for the use of the unapproved products bamlanivimab/ etesevimab to treat COVID-19

Bamlanivimab/etesevimab are investigational drugs that have not been approved by the FDA for any use; and should not be considered the standard of care for treatment of patients with COVID-19

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This use is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use, unless the authorization is terminated or revoked sooner

Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS related to bamlanivimab/etesevimab
Reminder | CDC variants of concern and other lineages by state

Providers should assess variant prevalence in their geographic area when choosing mAb therapeutic

- Estimated biweekly proportions of the most common SARS-CoV-2 lineages circulating in the U.S available from the CDC variant proportions data tracker

- Information on variants of concern updated in Section 15 of FDA fact sheets

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**Table 1: Unweighted Proportions of Variants of Concern and Other Lineages by State or Jurisdiction**

<table>
<thead>
<tr>
<th>State</th>
<th>B.1.1.7</th>
<th>B.1.351</th>
<th>B.1.427 / B.1.429</th>
<th>P.1</th>
<th>Other lineages</th>
<th>Total Available Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona</td>
<td>54.1%</td>
<td>1.1%</td>
<td>15.0%</td>
<td>6.6%</td>
<td>23.2%</td>
<td>627</td>
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<tr>
<td>California</td>
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<td>0.7%</td>
<td>21.0%</td>
<td>7.0%</td>
<td>25.9%</td>
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<td>Colorado</td>
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<td>0.4%</td>
<td>15.9%</td>
<td>2.8%</td>
<td>20.0%</td>
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<td>Connecticut</td>
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<td>0.6%</td>
<td>1.1%</td>
<td>2.6%</td>
<td>45.0%</td>
<td>1,175</td>
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<td>Florida</td>
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<td>0.2%</td>
<td>2.5%</td>
<td>7.6%</td>
<td>22.0%</td>
<td>10,208</td>
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<tr>
<td>Georgia</td>
<td>76.6%</td>
<td>1.9%</td>
<td>2.4%</td>
<td>2.3%</td>
<td>16.8%</td>
<td>1,420</td>
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<td>Illinois</td>
<td>55.6%</td>
<td>0.7%</td>
<td>6.1%</td>
<td>20.5%</td>
<td>17.1%</td>
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<td>Indiana</td>
<td>64.5%</td>
<td>0.7%</td>
<td>3.9%</td>
<td>7.5%</td>
<td>23.5%</td>
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<tr>
<td>Kentucky</td>
<td>63.7%</td>
<td>0.2%</td>
<td>2.2%</td>
<td>2.9%</td>
<td>29.0%</td>
<td>471</td>
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<tr>
<td>Michigan</td>
<td>67.9%</td>
<td>1.3%</td>
<td>1.2%</td>
<td>1.2%</td>
<td>29.1%</td>
<td>1,374</td>
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<tr>
<td>Massachusetts</td>
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<td>0.1%</td>
<td>1.9%</td>
<td>10.6%</td>
<td>36.5%</td>
<td>5,542</td>
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<tr>
<td>Michigan</td>
<td>77.4%</td>
<td>0.8%</td>
<td>1.9%</td>
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<td>Minnesota</td>
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<td>1.0%</td>
<td>7.0%</td>
<td>1.0%</td>
<td>14.8%</td>
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<tr>
<td>Missouri</td>
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<td>0.7%</td>
<td>3.2%</td>
<td>4.4%</td>
<td>20.1%</td>
<td>434</td>
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<tr>
<td>New Hampshire</td>
<td>59.5%</td>
<td>1.1%</td>
<td>14.4%</td>
<td>3.8%</td>
<td>23.5%</td>
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<td>New Hampshire</td>
<td>42.3%</td>
<td>0.3%</td>
<td>6.7%</td>
<td>6.0%</td>
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<tr>
<td>New Jersey</td>
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<td>0.9%</td>
<td>2.4%</td>
<td>48.8%</td>
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<tr>
<td>New York</td>
<td>48.3%</td>
<td>0.8%</td>
<td>2.3%</td>
<td>2.0%</td>
<td>44.2%</td>
<td>2,988</td>
</tr>
<tr>
<td>North Carolina</td>
<td>59.0%</td>
<td>2.0%</td>
<td>2.0%</td>
<td>1.2%</td>
<td>35.7%</td>
<td>1,867</td>
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<tr>
<td>Ohio</td>
<td>71.1%</td>
<td>1.4%</td>
<td>2.6%</td>
<td>2.8%</td>
<td>21.9%</td>
<td>1,413</td>
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<td>Oregon</td>
<td>38.0%</td>
<td>4.6%</td>
<td>25.3%</td>
<td>4.2%</td>
<td>27.0%</td>
<td>549</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>63.2%</td>
<td>0.9%</td>
<td>1.9%</td>
<td>2.0%</td>
<td>39.0%</td>
<td>8,500</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>68.8%</td>
<td>0.7%</td>
<td>2.1%</td>
<td>2.8%</td>
<td>28.4%</td>
<td>3,040</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>45.5%</td>
<td>0.5%</td>
<td>3.8%</td>
<td>5.8%</td>
<td>43.7%</td>
<td>1,271</td>
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<td>Tennessee</td>
<td>82.2%</td>
<td>0.5%</td>
<td>1.6%</td>
<td>1.5%</td>
<td>13.8%</td>
<td>1,289</td>
</tr>
<tr>
<td>Texas</td>
<td>77.7%</td>
<td>0.2%</td>
<td>3.4%</td>
<td>4.5%</td>
<td>19.2%</td>
<td>3,455</td>
</tr>
<tr>
<td>Virginia</td>
<td>70.0%</td>
<td>1.5%</td>
<td>1.9%</td>
<td>1.2%</td>
<td>24.5%</td>
<td>955</td>
</tr>
<tr>
<td>Washington</td>
<td>47.4%</td>
<td>0.9%</td>
<td>23.3%</td>
<td>5.9%</td>
<td>25.3%</td>
<td>439</td>
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<tr>
<td>West Virginia</td>
<td>56.1%</td>
<td>0.0%</td>
<td>0.3%</td>
<td>0.3%</td>
<td>3.3%</td>
<td>24,191</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>56.2%</td>
<td>1.1%</td>
<td>7.3%</td>
<td>4.6%</td>
<td>28.8%</td>
<td>1,027</td>
</tr>
</tbody>
</table>

Updated May 16, 2021

Variants proportions are based on representative CDC sequence data (NE2 + CDC-funded contract sequencing) collected over a 4-week period ending April 24, 2021 for states with at least 300 sequences.

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1. FDA factsheets: https://www.fda.gov/media/145611/download; https://www.fda.gov/media/145802/download
3. Table 2: Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

<table>
<thead>
<tr>
<th>Lineage with Spike Protein Substitution</th>
<th>Key Substitutions Tested</th>
<th>Fold Reduction in Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7 (UK origin)</td>
<td>N501Y</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.351 (South Africa origin)</td>
<td>K417N, E484K, N501Y*</td>
<td>no change</td>
</tr>
<tr>
<td>P.1 (Brazil origin)</td>
<td>K417T + E484K</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.427/B.1.429 (California origin)</td>
<td>L452R</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.526 (New York origin)*</td>
<td>E484K</td>
<td>no change</td>
</tr>
</tbody>
</table>

*Pseudoviruses expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: B.1.351: N501Y, B.1.427/B.1.429: N501Y; P.1 (Brazil): N501Y; B.1.526: E484K.

No change: <+2-fold reduction in susceptibility.

Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

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4. Table 3: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

<table>
<thead>
<tr>
<th>Lineage with Spike Protein Substitution</th>
<th>Key Substitutions Tested</th>
<th>Fold Reduction in Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7 (UK origin)</td>
<td>N501Y</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.351 (South Africa origin)</td>
<td>K417N, E484K, N501Y*</td>
<td>no change</td>
</tr>
<tr>
<td>P.1 (Brazil origin)</td>
<td>K417T + E484K</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.427/B.1.429 (California origin)</td>
<td>L452R</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.526 (New York origin)*</td>
<td>E484K</td>
<td>no change</td>
</tr>
</tbody>
</table>

*For variants with more than one substitution of concern, only the substitution(s) with the greatest impact on activity were tested. For B.1.351: P.1, and B.1.427/B.1.429, spike variants reflective of the consensus sequence for the lineage were tested.

No change: <+2-fold reduction in susceptibility.

Bamlanivimab and etesevimab together are unlikely to be active against variants with more than one substitution of concern.
Based on what we have learned to date - early administration of treatment needs fast testing turnaround and patient scheduling. Planning required for "Test and treat" or "Test and refer" models.

Overview
- Treatment likely most beneficial to patients if given early in symptom progression
- EUA requires administration of treatment as soon as possible after confirmed positive test result and within 10 days of symptom onset
- Strong partnership and communication between patients and HCP to get right treatment to right patients at right time
- Fast testing turnaround needed, to efficiently identify positive tests and schedule for treatment

Example of timeline which would fulfill EUA requirements

<table>
<thead>
<tr>
<th>Onset of symptoms</th>
<th>Clinical visit and diagnostic test</th>
<th>Confirmed positive test</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3 days post symptom onset</td>
<td>≤ 2 days post diagnostic test</td>
<td>≤3 days post positive test result</td>
<td></td>
</tr>
</tbody>
</table>

Treatment needed within 10 days of symptom onset. Testing sites should recommend COVID+ patients that are high risk confer with their HCP on potential suitability for Tx.

Please reference EUA factsheet for specific treatment guidelines including recommended treatment window.
Key challenges to overcome to allow for successful administration of mAb in outpatient setting

Drug ordering and storage

Out of scope of this playbook

For Additional Information on Ordering Monoclonal Antibodies:

https://www.phe.gov/emergency/events/COVID19/healthcare-facilities/Pages/default.aspx#step3

Key challenges for administration and strategies for success

- Many sites are not traditionally outfitted to do infusions in outpatient setting (besides hospitals and ERs), however successful models have been demonstrated in a variety of outpatient settings (stand-alone mAb infusion sites, skilled nursing facilities, and home infusion)
- Existing infusion centers currently treat immune-compromised patients and may not be the logical site for COVID-19 treatment
- Length of infusion process (infusion time may be up to ~1 hour infusion\(^1\) followed by 1 hour post-infusion monitoring) needing dedicated space and personnel. EUA revisions have allowed shorter infusion times. Patients must still be monitored for 1 hour post infusion
- Quick turn-around time for testing needed to diagnose patients within window for treatment (on site testing expedites infusion capabilities)

Please reference EUA factsheet for specific treatment guidelines

1. Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
Federal Monoclonal Antibody Playbook

Objective to summarize requirements to administer monoclonal antibodies for healthcare facilities interested in administering the product

Additional Resources Can be Found at
https://combatcovid.hhs.gov/
https://phe.gov

Product-specific playbooks for monoclonal antibody administration

Eli Lilly Bamlanivimab/Etezavimab Antibody Playbook
Objective to help sites of care operationalize a Bamlanivimab/Etezavimab antibody response to COVID-19 across varying infusion sites of care

Regeneron EUA guidebook
Provides additional detail on administration requirements for Regeneron mAbs product
Please note...

EUA guidelines continue to evolve

Please reference EUA fact-sheets for latest treatment guidelines and information

FDA continues to update dilution requirements and infusion times based on latest clinical information

Comprehensive checklist overview
Plan of action to administer monoclonal antibodies under outpatient EUA

Confirm your site wants to participate

- Review needs for treatment in outpatient settings
- Ensure site prepared to meet needs for treatment or willing to make required investments
- Confirm site leadership supportive of participation (including senior clinical leadership)
- Establish direct ordering account for monoclonal antibody product

Prepare your site and staff for outpatient mAbs administration

- Ensure sufficient supply of needed materials for treatment
  Infusion supplies, resuscitation equipment, etc.
- Develop staffing and personnel plan to support treatment
- Allocate needed facilities and equipment to support administration
- Ensure existing infection prevention plan sufficient
  - Adjust existing plan if needed to safely manage patient flow
  - Consider potential security requirements if needed
- Review drug administration needs with staff
- Review and establish reimbursement process
- Prepare for adverse events data tracking process

Develop procedures to identify and treat patients in timely manner

- Prepare for scheduling and routing of referrals from testing center or other sites to treatment
- Ensure infusion site staff and providers are aware of outpatient treatment availability
- Ensure patient privacy (HIPAA compliant) maintained during process
- Communicate to patient that EUA issued for investigational treatment but does not constitute research on behalf of the infusion site
Readiness checklist: Administration of outpatient mAbs under EUA

Allocate **dedicated space** and develop plan to **manage patient flow**
- Clear process for patients that are coming to clinical site including scheduling requirements
- Admission process for COVID-19 positive patients designed to minimize risk of spread per facility requirements / directions / guidelines
- Dedicated room available for treatment

Ensure **dedicated source of supplies**; which may be difficult to procure
Needed infusion components obtained
Example: IV kits, infusion chair, IV pole, vital sign monitoring equipment, emergency medications

Assign **sufficient personnel** to meet expected demand
Sufficient staffing plans in place for Nurse/IV tech, Provider, Pharmacist or other licensed medical professional
Likely need dedicated team to treat patients

Prepare for **drug administration** process
- Pre–visit: Clear treatment and monitoring plan developed for during infusion
- Treatment: Up to ~1-hour treatment\(^1\) and 1-hour post-treatment observation
  - Emergency protocol defined for addressing potential infusion reactions or complications
- Post-treatment: Clear process for patient follow-up defined using telemedicine as possible

Ensure **process for reimbursement** in place (non-drug administrative costs)

Prepare for **reporting needs** for adverse events and record keeping

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\(^1\) Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
Activity 1: Define facilities and patient visit logistics
Site will need dedicated outpatient COVID-19 treatment space

Dedicated COVID-19 patient area with needed infusion supplies
- Some sites using COVID-19 waiting rooms for monitoring post infusion
- Rededication of existing clinical space acceptable under CMS Hospital Without Walls Initiative

Immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the EMS, as necessary

Select recommendations for outpatient setting, for more information reference CDC guidelines https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html
As part of the CMS Hospital Without Walls initiative, hospitals can provide services outside of standard hospital settings:

- **Other healthcare facilities** (e.g., urgent care clinics, doctors' offices etc)
- **Remote locations or sites** not normally considered healthcare facilities, (e.g., patient home via telemedicine, hotels, community site, temporary tents)
- **Nursing home or home health services** also likely to be acceptable sites of administration

Alternate site of care will need **same core capabilities and supplies** as typical site of administration:

- Facility and patient flow needs (page 18 and 20 of this document)
- Supplies needed on site (e.g., rescue medication, infusion supplies, etc – page 27 of this document)

**Please reference CMS Hospitals Without Walls waivers and guidance for detailed information about program**
Important to manage patient flow in a healthcare setting

Ensure appropriate infection control practices in place based on latest CDC guidelines, e.g.:

- Have patient **wait to enter the site** until pre-scheduled time for treatment

- Ensure patient **wearing a mask or face covering** before entering the building

- Escort patient **directly to room, limit transport and movement of the patient outside of the room**

- As all patients treated are confirmed positive for COVID-19, **multiple patients may be treated simultaneously in one area**.

- Medical and support personnel entering room need to **wear sufficient PPE** based on CDC guidelines

- Room should undergo **appropriate cleaning and surface disinfection** before it is returned to routine use

Select recommendations for outpatient setting, for more information reference [CDC guidelines](https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html)
Infusion preparation process:
- Prepare sterile infusions in a manner consistent with local laws, regulations, guidelines and policies
- Obtain new vial(s) and/or IV bags if the drug product contains any visible particulate matter

Needs for space to prepare mAb drug:
Dedicated preparation area with sufficient capacity onsite or nearby

Acceptable equipment for mAb drug storage:
- Functional pharmacy sink
- Refrigerated storage (2-8° C)
- Temperature control mechanism including temperature monitoring process

Please see EUA manufacturer fact sheet for drug-specific requirements
Testing needs

Outpatient monoclonal antibody treatments are to be administered as soon as possible following positive test result, and within 10 days of symptom onset.

Fast turn-around testing capabilities key to identify patients and treat within this window:
- On-site point-of-care rapid testing or PCR tests ideal to provide quick diagnosis and treat patients on the same day.
- Alternatives include partnership with off-site testing facility nearby with reliable and quick turnaround and robust patient tracking and reporting mechanism.

Accelerated testing results turnaround likely recommended to allow for infusion early in disease progression.

Please reference EUA factsheet for **detailed treatment guidelines including recommended treatment window**

Distribution – Direct ordering for mAb products under EUA

- HHS/ASPR continues to manage the distribution of mAb products under EUA as stated in the FDA Letters of Authorization.

- Given the current supply of product, casirivimab / imdevimab and bamlanivimab / etesevimab can be requested via direct ordering for all sites (no further allocations to states are currently planned).

- Direct orders for casirivimab / imdevimab and bamlanivimab / etesevimab are limited to 48 patient courses per site/per week, though sites with higher utilization can request additional courses.

- Questions regarding the direct order process: HHS: COVID19Therapeutics@hhs.gov

Information on direct order process available at phe.gov –

Product will be shipped refrigerated (2-8° C) to your location by USG distribution partners.

Product should be stored refrigerated (2-8° C) before use.

Target shelf-life for product ~10 months at minimum, follow guidance from manufacturer on expiration dates and product turnover.

Prepared IV solutions are intended for immediate patient administration. If not used immediately:
- Solutions may be held at refrigerated conditions for example
  - Eli Lilly no more than 24 hours
  - Regeneron no more than 36 hours
- Solutions may be held at ambient light and room temperature conditions (including preparation, solution hold, infusion and flush) for example
  - Eli Lilly no more than 7 hours
  - Regeneron no more than 5 hours

Please adhere to all guidelines for storage and use provided by manufacturer of EUA product.
Activity 2: Ensure sufficient supplies
Site supplies needed: Standard infusion supplies are needed but several components have been difficult to source

Sites interested in providing outpatient infusions of mAbs to COVID+ patients should:

1. Confirm sufficient supplies of infusion materials
2. Proactively ensure items with long-lead times are sourced for your site

Ensure supplies sufficient to cover mAbs treatment in addition to day-to-day operations needs

<table>
<thead>
<tr>
<th>PPE</th>
<th>Infusion supplies</th>
<th>General supplies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gloves</td>
<td>• Infusion chairs – recommended only</td>
<td>• Infusion Reaction Kit</td>
</tr>
<tr>
<td>• Gowns</td>
<td>• IV pole</td>
<td>• Vital signs equipment</td>
</tr>
<tr>
<td>• Eye and face protection (e.g. goggles, safety glasses, face shields)</td>
<td>• IV administration sets</td>
<td>• Crash cart or Emergency Medical Management Equipment and Backboard</td>
</tr>
<tr>
<td>• NIOSH-certified, disposable N95 filter facepiece respirators or better</td>
<td>PVC infusion set with/without DEHP containing 0.2 or 0.22 micron polyethersulfone (PES) in-line filter</td>
<td>• Refrigerator Optional to store prepared solution onsite</td>
</tr>
<tr>
<td></td>
<td>• IV and catheters</td>
<td>• Privacy screens</td>
</tr>
<tr>
<td></td>
<td>• 3mL saline syringes</td>
<td>• Biohazard disposal bag</td>
</tr>
<tr>
<td></td>
<td>• Appropriately sized syringes</td>
<td>• Disposable disinfecting wipes</td>
</tr>
<tr>
<td></td>
<td>• Alcohol wipes</td>
<td>• Thermometer probe covers (if required)</td>
</tr>
<tr>
<td></td>
<td>• 2x2 gauze pads</td>
<td>• 70% alcohol wipes</td>
</tr>
<tr>
<td></td>
<td>• Adhesive bandages</td>
<td>• Paper towels</td>
</tr>
<tr>
<td></td>
<td>• Tegaderm bio-occlusive dressing</td>
<td>• Trash bins and liners</td>
</tr>
<tr>
<td></td>
<td>• Absorbent underpads (blue pads)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Extension set tubing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Needles – stainless steel 18ga</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sharps containers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Transpore tape</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Transilluminator (vein finder)</td>
<td></td>
</tr>
</tbody>
</table>

List of suggested supplies (not exhaustive)

Please reference EUA factsheet for final requirements
Activity 3: Develop plan for staffing and personnel
Treating patients needs support of...

Prescribe monoclonal antibody to patient, answer questions and respond in case of emergency
- Licensed healthcare provider (MD/PA/NP)
- HCP will need to be on site or available via telehealth or phone for treatment
- At least 1 team member (nurse or healthcare provider) onsite should be able to respond to medical emergency (e.g., severe infusion reaction); any specific certifications based on state and healthcare facility regulations and policies

Prepare the infusion, answer questions and support with monoclonal antibody storage
- Pharmacy does not need to be physically located at the site of infusion
- Note the infusion can be prepared by any qualified medical professional

Administer patient infusion (up to ~1 hr) and monitor patient wellbeing (1 hr)
- May require 2 nurses to start infusion, nurse practitioner to oversee larger infusion unit (if needed)
- Experienced phlebotomist needed as often difficult to find vein in patients (often high BMI and dehydrated)

Please reference EUA factsheet for specific treatment guidelines including dilution and infusion time
# Needed roles and responsibilities for site

<table>
<thead>
<tr>
<th>Role</th>
<th>Needed skills/profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient intake</td>
<td>Scheduling and administrative skills</td>
</tr>
<tr>
<td>Drug preparation</td>
<td>Pharmacist, pharmacy technician, or nurse or other HCP trained in IV preparation</td>
</tr>
<tr>
<td>Infusion: Start IV</td>
<td>Nurse or other alternate healthcare team member trained to begin an IV</td>
</tr>
<tr>
<td>Infusion: Administer infusion</td>
<td>Nurse or other alternate healthcare team member trained in administering an IV</td>
</tr>
<tr>
<td>Infusion monitoring</td>
<td>Nurse or other alternate healthcare team member trained in vital sign monitoring</td>
</tr>
<tr>
<td>Post infusion observation</td>
<td>Nurse or other alternate healthcare team member trained in vital sign monitoring</td>
</tr>
<tr>
<td>Patient release</td>
<td>Administrative skills, or nurse or other alternate healthcare team member as required</td>
</tr>
<tr>
<td>Cleaning</td>
<td>Person trained in COVID cleaning / disinfection</td>
</tr>
</tbody>
</table>
Activity 4: Review drug administration process
Three potential treatment pathways for symptomatic COVID-19 patients to receive care

**Scenario 1**
Patient tests positive and referred to site:
- Treatment scheduled for infusion as soon as possible following result
- Patient counseled and assents to treatment (if not completed earlier in process), then treated via infusion
- Patient completes monitoring and leaves the facility, telemedicine follow-up

**Scenario 2**
Patient arrives for testing at site with unknown diagnosis:
- Point-of-care testing performed, patient awaits results onsite
- Treatment scheduled for same day infusion
- Patient counseled and assents to treatment (if not completed earlier in process), then treated via infusion
- Patient completes monitoring and leaves the facility, telemedicine follow-up

**Scenario 3**
Patient arrives for testing at site with unknown diagnosis:
- Patient tested, treatment discussed, sent home to await results
- If positive, proactive outreach to patients and treatment scheduled for infusion as soon as possible following result
- Treatment needed as soon as possible following positive test result and ≤10 days from onset of symptoms
- Please reference EUA factsheet for exact treatment window
**Patient flow for outpatient mAbs product**

**Scenario 1: Confirmed positive patient referred for treatment**

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>Treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
</table>
| Confirm documentation of COVID-19 infection via either  
  - Participant-provided lab report  
  - Medical record lab report  
  - Direct communication from a provider or laboratory  
  **Discuss treatment with patient**  
  Ensure patient meets treatment requirements and understands risks  
  **Schedule the patient to come in for treatment ASAP**  
  - Provide guidance on site visit protocols to patients  
  - Provide patient education on what to expect with infusions  
  **Pre-treatment steps should be completed via telemedicine as possible (~30 mins)** |  
  **Pre-book time for infusion space and follow clear protocol for coming onsite**  
  - Ensure operationally ready to receive and treat the patient  
  - Use CDC recommended practices to minimize exposure to others  
  **Provide treatment to patient**  
  - Infusion duration up to ~1 hr\(^1\) with an additional 1 hr of observation post infusion (checks during infusion and observation)  
  - Infusion pumps or gravity-based infusion acceptable  
  - Ensure adequate staffing  
  **Ensure preparation for infusion reactions as unlikely but possible side effect**  
  - Infusion rate may be reduced based on patient circumstances  
  - Ensure emergency action plan in place; ability to activate EMS if necessary, a requirement for administration under EUA |  
  **Discharge patient immediately following monitoring completion**  
  Follow clear protocol to minimize risk of exposure to others  
  **Post-treatment care encouraged to be via telemedicine as possible**  
  Normal follow-up care, no special data tracking requirements  

---

\(^1\) Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
Patient flow for outpatient mAbs product

**Scenario 2 and 3: Patient arrives for testing at site with unknown diagnosis**

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>Treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
</table>

**Direct patient to typical testing process for site (onsite or offsite)**
Quick response testing needed for early diagnosis to enable early treatment

**Assuming patient discharged to await test results, once patient confirmed positive outreach on treatment (~30 mins)**:
- Discuss treatment with patient
  - Ensure patient meets treatment requirements and understands risks
  - Provide guidance on infusions and site visit protocols to patients
- Schedule the patient to come in for treatment ASAP
- Pre-treatment discussion and scheduling should be via telemedicine as possible

**In case of point-of-care rapid testing, consider same-day infusions. Needs**
- Isolated location for patient to wait
- Availability of infusion space and staff

**Pre-book time for infusion space and follow clear protocol for coming onsite**
- Ensure operationally ready to receive and treat the patient
- Use CDC recommended practices to minimize exposure to others

**Provide treatment to patient**
- Infusion duration up to ~1 hr\(^1\) with an additional 1 hr of observation post infusion (checks during infusion and observation)
- Infusion pumps or gravity-based infusion acceptable
- Ensure adequate staffing

**Ensure preparation for infusion reactions as unlikely but possible side effect**
- Infusion rate may be reduced based on patient circumstances
- Ensure emergency action plan in place; ability to activate EMS if necessary, a requirement for administration under EUA

**Discharge patient immediately following monitoring completion**
Follow clear protocol to minimize risk of exposure to others

**Post-treatment care encouraged to be via telemedicine as possible**
Normal follow-up care, no special data tracking requirements

---

1. Contingent on product dilution, reference EUA fact sheet for dilution and infusion timing
General Guidelines for bamlanivimab/etesevimab Dosing, Dilution, and Administration

Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion in Patients Weighing 50 kg or More

<table>
<thead>
<tr>
<th>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</th>
<th>Maximum Infusion Rate</th>
<th>Minimum Infusion Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL</td>
<td>310 mL/hr</td>
<td>21 minutes</td>
</tr>
<tr>
<td>100 mL</td>
<td>310 mL/hr</td>
<td>31 minutes</td>
</tr>
<tr>
<td>150 mL</td>
<td>310 mL/hr</td>
<td>41 minutes</td>
</tr>
<tr>
<td>250 mL</td>
<td>310 mL/hr</td>
<td>60 minutes</td>
</tr>
</tbody>
</table>

*700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion in Patients Weighing Less Than 50 kg

<table>
<thead>
<tr>
<th>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</th>
<th>Maximum Infusion Rate</th>
<th>Minimum Infusion Time</th>
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<tbody>
<tr>
<td>50 mL</td>
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<tr>
<td>100 mL</td>
<td>310 mL/hr</td>
<td>31 minutes</td>
</tr>
<tr>
<td>150 mL</td>
<td>310 mL/hr</td>
<td>41 minutes</td>
</tr>
</tbody>
</table>

Notes for Eli Lilly: BAMLANIVIMAB MUST BE ADMINISTERED TOGETHER WITH ETESEVIMAB AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY. Note: not all 50mL & 100mL saline bags will allow addition of 60mL of bam / ete – ensure bag allows for mixing

General Guidelines for REGEN-COV Dosing, Dilution, and Administration

Notes for Regeneron: CASIRIVIMAB AND IMDEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.

Dose packs for REGEN-COV (casirivimab and imdevimab)

New packaging presentation of casirivimab and imdevimab containing one treatment dose of REGEN-COV began in February 2021

Each REGEN-COV Dose Pack is delivered in a plastic bag and contains:

- **Sufficient number of vials** of casirivimab (REGN10933) and imdevimab (REGN10987) to prepare one treatment dose – since both casirivimab and imdevimab are available in different sizes, REGEN-COV Dose Packs may contain **2, 5 or 8 vials**
- A **1-page Information Sheet**
- A sticker on bag with name REGEN-COV and the NDC based on the combination of cartons contained within the dose pack

In addition to REGEN-COV Dose Packs, single cartons of casirivimab and imdevimab will still be in distribution – see next page for examples
Activity 5: Prepare for reimbursement and ordering
Follow process for direct ordering procedures to receive mAb product

Under initial phase of treatment, **drug cost likely to be paid by US government** under advanced purchase agreements

Confirm internally with your site administration on reimbursement for **non-drug costs** (e.g., infusion services, pharmacy)

Please reference CMS resources for more information

**CMS Monoclonal Reimbursement**

**COVID FAQs:**
CMS: Coverage of Monoclonal Antibody Products to Treat COVID-19

Medicare

<table>
<thead>
<tr>
<th>Site of Care1</th>
<th>Payable by Medicare</th>
<th>Expected Patient Cost-Sharing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient Hospital</td>
<td>✓</td>
<td>No patient cost-sharing</td>
</tr>
<tr>
<td>Outpatient Hospital or &quot;Hospital without Walls&quot;2</td>
<td>✓</td>
<td>No patient cost-sharing</td>
</tr>
<tr>
<td>Outpatient Physician Office/Infusion Center</td>
<td>✓</td>
<td>No patient cost-sharing3</td>
</tr>
<tr>
<td>Nursing Home (See third bullet in Key Facts on CMS enforcement discretion)</td>
<td>✓</td>
<td>No patient cost-sharing</td>
</tr>
<tr>
<td>Home</td>
<td>✓</td>
<td>No patient cost-sharing</td>
</tr>
</tbody>
</table>

1Services must be furnished within the scope of the product’s FDA authorization or approval and within the provider’s scope of practice.
2Under the Hospital Without Walls initiative, hospitals can provide hospital services in other healthcare facilities and sites that would not otherwise be considered to be part of a healthcare facility, or can set up temporary expansion sites to help address the urgent need to increase capacity to care for patients.
3Cost-sharing may apply to Medicare beneficiaries when they receive care from a provider that doesn’t participate in Medicare.
4Certain monoclonal antibody products to treat COVID-19 have been authorized under Food and Drug Administration Emergency Use Authorizations since November 10, 2020. More information including the level II HCPCS codes for the administration/infusion and post-administration monitoring of these products can be found online in the Program Instruction.

Expected Payment to Providers: Key Facts

- Medicare payment for monoclonal antibody products to treat COVID-19 is similar across sites of care, with some small differences.
- Medicare pays for the administration of monoclonal antibody products to treat COVID-19. For example, Medicare will pay a national average of approximately $450 for the administration of certain monoclonal antibody products. Home infusion is reimbursed at a higher rate.
- CMS will exercise enforcement discretion to allow Medicare-enrolled immunizers working within their scope of practice and subject to applicable state law to bill directly and receive direct reimbursement from the Medicare program for administering monoclonal antibody treatments to Medicare Part A Skilled Nursing Facility residents.
- Medicare will pay the provider for these monoclonal antibody products when they are purchased by the provider. Medicare won’t pay if the product is given to the provider for free by, for example, a government entity.
- When purchased by the provider, Medicare payment is typically at reasonable cost or at 95% of the Average Wholesale Price (an amount determined by the manufacturer). These payment amounts vary depending on which type of provider is supplying the product. Original Medicare will pay for these products for beneficiaries enrolled in Medicare Advantage.
- For more specific information about Medicare payments to providers for these monoclonal antibody products, please see these Frequently Asked Questions.

Eli Lilly product codes

Q0245:
  • Long descriptor: Injection, bamlanivimab and etesevimab, 2100 mg
  • Short descriptor: bamlanivimab and etesevimab

M0245:
  • Long Descriptor: intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring
  • Short Descriptor: Bamlan and etesev infusion

M0246:
  • Long Descriptor: intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring in the home or residence
  • Short Descriptor: Bamlan and etesev infus home

Regeneron product codes

Q0243:
  • Long descriptor: Injection, casirivimab and imdevimab, 2400 mg
  • Short descriptor: casirivimab and imdevimab

M0243:
  • Long Descriptor: intravenous infusion, casirivimab and imdevimab includes infusion and post administration monitoring
  • Short Descriptor: casirivimab and imdevimab infusion

M0244:
  • Long Descriptor: intravenous infusion, casirivimab and imdevimab includes infusion and post administration monitoring in the home or residence
  • Short Descriptor: casirivi and imdevi infus home
Activity 6: Reporting process
Sites receiving monoclonal antibody will follow established mechanisms for tracking and reporting serious adverse events. Events that are potentially attributable to monoclonal antibody use must be reported to the FDA:
- Refer to the Fact Sheet for Healthcare Providers as part of EUA for guidance
- Complete and submit a MedWatch form or complete and fax FDA Form 3500 to report

Site must maintain records regarding use of the monoclonal antibody by patients:
- **Inventory information:** e.g., lot numbers, quantity, receiving site, receipt date, product storage
- **Patient information:** e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered

Ensure that any records associated with this EUA are maintained for inspection upon request.
Sites are required to report utilization of product to HHS through their state or TeleTracking system.

First-time users will receive enrollment and reporting instructions in an e-mail from protect-noreply@hhs.gov with the subject line of “Invitation: HHS TeleTracking COVID-19 Portal.”

This email provides step-by-step instructions to access the Portal for the first time.

If you do not receive an email in the next 48 hours, please contact TeleTracking Technical Support at hhs-protect@teletracking.com.