**BC COVID THERAPEUTICS COMMITTEE (CTC)**

# Clinical Practice Guide for the Use of REGEN-COV in Inpatients with COVID-19

## RECOMMENDATION

REGEN-COV (casirivimab + imdevimab) is RECOMMENDED for inpatients who are:

- Hospitalized with a confirmed SARS-COV-2 infection who are **severely ill** from symptoms of COVID-19 (see #1), AND
- Who can receive REGEN-COV **within 10 days of symptom onset** (see #2), AND
- Are **seronegative** for COVID-19 anti-spike antibody as confirmed by serological testing within the 10-day symptom window, irrespective of COVID-19 vaccine status (see #3) OR, if serology results are delayed, be very likely to be seronegative due to being (see #4):
    - **Unvaccinated or partially unvaccinated** (received 0 or 1 of 2 COVID-19 vaccine doses) with no prior history of COVID-19 infection, OR
    - **Unlikely to adequately respond to vaccination** despite two* COVID-19 vaccine doses due to:
        - Active treatment for solid tumor or hematological malignancies, OR
        - Having received a solid organ transplant and treated with immunosuppression, OR
        - Receiving CAR-T cell therapy or hematopoietic stem cell transplant within the last 2 years, OR
        - Having a moderate to severe primary immunodeficiency, OR
        - Having advanced untreated HIV or AIDS, OR
        - Active receipt of anti-B cell therapies (e.g. rituximab, ocrelizumab, obinutuzumab), high-dose systemic steroids (=20mg prednisone equivalent daily for at least 14 days), alkylating agents (e.g. cyclophosphamide, cisplatin), antimetabolites (e.g. methotrexate, 5-FU) or anti-TNF agents (e.g. infliximab, adalimumab)
        - *Such patients, upon receipt of a third dose of a COVID-19 vaccine may or may not adequately respond to vaccination. Case-by-case evaluation with an expert is recommended. Serology will likely be required for confirmation.

The recommended regimen is **2.4g IV x 1 dose of REGEN-COV** (1.2g casirivimab + 1.2g imdevimab) (see #5)

This therapy does not replace other agents which used for treatment of COVID-19 (see #6).

Patients should be informed that REGEN-COV does not have full Health Canada approval for this indication and consent should be obtained (see #7). Particular care should be taken to inform pregnant patients (see #8).

## Role of REGEN-COV in inpatient settings

REGEN-COV, or REGENERON, is a combination of two antibodies, casirivimab and imdevimab that act to

neutralize the spike protein of the SARS-COV-2 virus, hindering cell entry and replication. REGN-COV-2 is active against all known variants of concern, including delta.

Evidence Summary

REGEN-COV has been evaluated in various clinical settings, including mild COVID-19 and post-exposure prophylaxis; however, the largest benefit was observed in studies of severely ill inpatients. *A large, investigator-initiated randomized controlled trial (RECOVERY)[1] showed that the Number-Needed-to-Treat to prevent one death by giving REGEN-COV to this population is 17*. The trial also showed a reduction in the risk of needing mechanical ventilation and duration of hospitalization. A recently published Phase II/III trial conducted by the manufacturer[2] gives preliminary confirmation of these results.

Drug Supply

As the drug supply is limited, REGEN-COV in BC has been reserved for who are hospitalized with confirmed SARS-COV-2 infection due to symptoms of COVID-19 and are severely ill.

**Practice Point #1: Definition of severely ill**

Severely ill patients are those who are hospitalized due to symptoms of confirmed COVID-19 and who are:

- Receiving low flow supplemental oxygen through nasal prongs, OR
- Receiving hi-flow supplemental oxygen if flow rate ≤ 30 L/min and FiO2 ≤ 0.4

**BUT NOT**

- Receiving hi-flow supplemental oxygen if flow rate > 30 L/min and FiO2 > 0.4, OR
- Invasive or non-invasive ventilation, OR
- Vasopressor or inotropic support

Patient Location

Patients who are candidates for REGEN-COV are usually located on the inpatient ward, and not in Intensive Care settings. Those who are not requiring supplemental oxygen are considered mildly ill and are not candidates for REGEN-COV.

Evidence Summary

Evidence has demonstrated that the benefit of REGEN-COV in inpatients is limited to this population. In RECOVERY[1], the OR for mortality in severely ill patients was 0.81 (0.68–0.97) but was not statistically significant in those receiving non-invasive or invasive ventilation (OR=0.86 (0.68–1.08) and 0.71 (0.35–1.47), respectively). The manufacturer-sponsored study[2] opted to exclude critically ill patients, citing that the benefit in this population is unlikely. Other trials of COVID-19-specific monoclonal antibodies have either showed no benefit or a trend towards harm in critically ill patients[3,4,5]. In its monograph, the manufacturer states that "monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation" and advises against the use of REGEN-COV in this sub-group[6].

**Practice Point Summary: REGEN-COV is recommended in hospitalized patients with a confirmed SARS-COV-2 infection who are severely ill from symptoms of COVID-19.**

**Practice Point #2: Timing of administration from symptom onset**

Shortly after infection, unimmunized patients begin producing antibodies as part of the innate immune response. This process has been documented to occur after 5-10 days from symptom onset. As such, the benefit of exogenous anti-COVID-19 antibodies to neutralize the virus and prevent replication has a narrow timeframe, after which additional antibodies have little to no effect.

Evidence Summary

In the RECOVERY trial, patients who were 7 days or less from symptom onset at the time of hospitalization saw a statistically significant reduction in mortality (OR 0.76 (0.64−0.91)), but those who presented later did not (OR 0.83 (0.67−1.03)). Under usual clinical trial procedures, patients would have received REGEN-COV within the next few days following presentation to hospital, hence why 10 days from symptom onset has been chosen. The manufacturer-sponsored trial subsequently used 10 days or less from symptom onset as a key inclusion criterion for their study and excluded patients who have been sick for longer.

Immunocompromised Patients

Certain patients, such as those who are very severely immunocompromised (see #4), may never develop antibodies from vaccination or natural infection, regardless of the duration of their illness. Administering REGEN-COV to such patients more than 10 days from symptom onset should only be endeavoured with expert consultation.

**Practice Point Summary: REGEN-COV is recommended only to those who can receive REGEN-COV within 10 days of symptom onset.**

**Practice Point #3: Serology testing**

The benefit of REGEN-COV in severely ill patients is limited to those who are seronegative; additional antibodies given to those who are already producing their own humoral response has been shown to be futile.

Evidence Summary

In RECOVERY, the primary endpoint of mortality was evaluated only in seronegative trial participants. The OR was 0.80 (0.70−0.91), p=0.0010, whereas it was not statistically significant in the subgroup of seropositive patients (OR= 1.09 (0.95−1.26)). The manufacturer-conducted trial showed preliminary phase III results confirming the findings of RECOVERY: the proportion of patients who died or required mechanical ventilation from day 6 to day 29 was 47.1% lower (15% vs. 7.9%; CI 10.2-68.8%) in seronegative patients, whereas it was not statistically significant when seropositive and seronegative patients were analysed together.

In both trials, the proportion of all-comers who were seronegative was only 47.6% and 34%, despite the trials being conducted before vaccinations were widely available, indicating that natural seroconversion is rapid. Due to the cost of REGEN-COV and its lack of benefit in seropositive patients, the drug cannot be given indiscriminately and serostatus is required to maximize cost-effectiveness. Some studies also showed a trend towards harm in seropositive patients; while these findings are not statistically significant, harm has not been definitively excluded.

Testing in BC

Serology testing will be offered to all inpatients meeting clinical criteria for REGEN-COV administration. Many Health Authorities will be using the current transport mechanisms to send samples to BCCDC; some hospitals will be offering serology in-house. Anti-spike IgG only will be used to confer serostatus as per the RECOVERY protocol; anti-nucleocapsid antibody will not be tested. Serostatus will be reported qualitatively (positive or negative) and not quantified.

Turn-Around Times

Turn-around times vary by patient location. To ensure timely administration of REGEN-COV within 10 days of symptom onset, the following guide for ordering serology was developed by provincial laboratory leaders:

Table 1: Estimated Turn-Around-Times in BC

| Location of testing site with respect to ordering site | Turn-Around-Time | Max time from symptom onset when serology should be ordered |
|---|---|---|
| Serology is available on site | 1-2 days | 8-9 days |
| Serology is available at a geographically proximal facility | 1-2 days | 8-9 days |
| Serology is available at a geographically remote facility, but with direct sample transport option | 2-3 days | 7-8 days |
| Serology is available at a geographically remote facility and sample must be carried by 2 separate couriers | 3-4 days | 6-7 days |

Please contact your **local medical microbiologist on-call** for questions and specifics regarding serology orders.

Vaccinated vs. Unvaccinated Patients

While it is predicted that fully vaccinated patients are less likely to be seronegative, the exact proportion of those who do not sero-convert or who have waning antibodies is unknown. At this time, laboratory leaders have committed to offer testing to both vaccinated and unvaccinated patients but will examine if vaccination status warrants exclusion from serotesting as data become available.

Previous receipt of anti-COVID-19 monoclonal antibodies

Monoclonal antibodies against COVID-19 (e.g. sotrovimab) can also be used in mildly ill patients, usually in ambulatory settings, to prevent hospitalization. These antibodies can last 3-6 months after administration. Patients who are within 3 months of receiving mAbs for treatment of COVID-19 should not receive REGEN-COV or be serotested should they become severely ill with COVID-19.

**Practice Point Summary: REGEN-COV is recommended only in patients seronegative for COVID-19 anti-spike antibody as confirmed by serological testing, irrespective of COVID-19 vaccine status.**

**Practice Point #4: Administering REGEN-COV without serology results**

Certain exceptional situations warrant administration of REGEN-COV without confirmed serology results.

As currently available turn-around-times may not produce results for a number of days, patients who are

***deteriorating to the point of requiring imminent critical illness* AND *are likely to be seronegative due to inadequate or no vaccination or vaccine response, with no prior history of COVID-19*** may be considered for administration of REGEN-COV before serostatus is confirmed, or when serology is delayed (e.g. due to extreme weather events impeding transport). This includes:

- Patients who are severely ill but are **deteriorating clinically and are about to become critically ill**:
    - Requiring organ support in the form of hi-flow supplemental oxygen if flow rate > 30 L/min and FiO2 > 0.4, OR
    - Invasive or non-invasive ventilation, OR
    - Vasopressor or inotropic support

AND

- Are **unvaccinated or partially unvaccinated** (received none or 1 of 2 COVID-19 vaccine doses) with no prior history of COVID-19 infection OR
- Are **unlikely to adequately respond to vaccination** despite two COVID-19 vaccine doses* due to:
    - Active treatment for solid tumor or hematological malignancies, OR
    - Having received a solid organ transplant and treated with immunosuppression, OR
    - Receiving CAR-T cell therapy or hematopoietic stem cell transplant within the last 2 years, OR
    - Having a moderate to severe primary immunodeficiency, OR
    - Having advanced untreated HIV or AIDS, OR
    - Active receipt of anti-B cell therapies (e.g. rituximab, ocrelizumab, obinutuzumab), high-dose systemic steroids (=20mg prednisone equivalent daily for at least 14 days), alkylating agents (e.g. cyclophosphamide, cisplatin), antimetabolites (e.g. methotrexate, 5-FU) or anti-TNF agents (e.g. infliximab, adalimumab)
    - *Such patients, upon receipt of a third dose of a COVID-19 vaccine may or may not adequately respond to vaccination. Case-by-case evaluation with an expert is recommended. Serology will likely be required for confirmation.

Criteria that define patients unlikely to adequately respond to vaccination were developed by the National Advisory Committee for Vaccination (NACI) to prioritize this vulnerable group of patients for third doses of the COVID-19 vaccine.

All efforts should be made to order serology on all in-patients being considered for REGEN-COV and to administer REGEN-COV before critically ill criteria are met.

**Practice Point Summary: Patients who are deteriorating to the point of requiring imminent organ support AND are likely to be seronegative due to inadequate vaccination may be considered for administration of REGEN-COV before serostatus is confirmed**.

**Practice Point #5: Dose of REGEN-COV**

The RECOVERY trial used a single dose of REGEN-COV of 8g (casirivimab 4g + imdevimab 4g). This trial occurred at a time when the lowest effective dose of REGEN-COV was not known. Since its publication, various other studies have shown that REGEN-COV produces a flat dose-response, and clinical efficaciousness does not change significantly depending on the dose use. Recently, the manufacturer has demonstrated that when compared to the 8g dose, 2.4g of REGEN-COV resulted in equivalent virological and clinical endpoints

when used in severely ill hospitalized patients.

REGEN-COV comes supplied as a 2.4g dose (casirivimab 1.2g + imdevimab 1.2g) in single use vials. The 8g dose is not being pursued as a marketed product. To maximize cost-effectiveness and minimize wastage while ensuring efficacy, REGEN-COV should be dosed as a single dose of 2.4g (casirivimab 1.2g + imdevimab 1.2g).

**Practice Point Summary: The recommended regimen of REGEN-COV is a single 2.4g dose of REGEN-COV (1.2g casirivimab + 1.2g imdevimab)**

**Practice Point #6: REGEN-COV should not replace other agents which are standard of care for COVID-19**.

REGEN-COV has a unique mechanism of action and does not replace other therapies that may be use for treatment of severely ill patients with COVID-19. Such patients usually receive:

- Dexamethasone or another steroid
- Therapeutic anticoagulation, and
- May infrequently receive remdesivir

REGEN-COV has been evaluated in addition to these therapies in clinical studies. It poses no drug interactions or additional safety concerns when given with these agents. There is no evidence to support the use of REGEN-COV as an alternative to other COVID-19 therapies that may be in short supply (e.g. tocilizumab).

**Practice Point Summary: REGEN-COV does not replace other agents used for treatment of COVID-19.**

**Practice Point #7: Informed consent for REGEN-COV**

As stated by the manufacturer, the use of REGEN-COV (casirivimab and imdevimab) is permitted under an interim authorization delivered in accordance with section 5 of the COVID-19 Interim order (IO)[7] , pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information on an authorization under this pathway, clinicians can refer to Health Canada's IO Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19[7].

**Practice Point Summary: Patients should be informed that REGEN-COV does not have full Health Canada approval for this indication and consent should be obtained.**

**Practice Point #8: REGEN-COV and Pregnancy**

Pregnant patients were not excluded from the RECOVERY trial. There were 25 pregnant patients randomized to receive REGEN-COV or placebo[1]. In the product monograph, pregnancy is not listed as a contraindication; the manufacturer addresses pregnancy in its dosing guidance recommending that no dose adjustments be made specifically for pregnancy[6].

As with many new drugs, there are limited data from the use of casirivimab with imdevimab in pregnant women. Animal reproductive toxicity studies have not been conducted. However, in a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, no binding of clinical concern was detected[6]. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown

whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing fetus. Combination casirivimab and imdevimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus considering all associated health factors[6].

Pregnancy is known to be an independent risk factor for maternal mortality, progression to ventilation and premature delivery. In the absence of other effective therapies besides corticosteroids, local experts agree that treatment with REGEN-COV can be offered as the reduction in mortality may justify the theoretical and unknown risk of treatment. Informed consent should be obtained from the patient and expert consultation with, for example, Maternal Fetal Medicine is recommended.

**Practice Point Summary: Pregnant patients should be informed of the risks and benefits of REGEN-COV and informed consent should be obtained in consultation with Maternal-Fetal Medicine**

References:


1. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv (https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1, accessed 16 Nov 2021)
2. Somersan-Karakaya S et al. REGEN-COV® for Treatment of Hospitalized Patients with Covid-19. medRxiv (https://www.medrxiv.org/content/10.1101/2021.11.05.21265656v2), accessed 16 Nov 2021
3. ACTIV-3/TICO LY-CoV555 Study Group. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med 2021; 384:905-914. DOI: 10.1056/NEJMoa2033130
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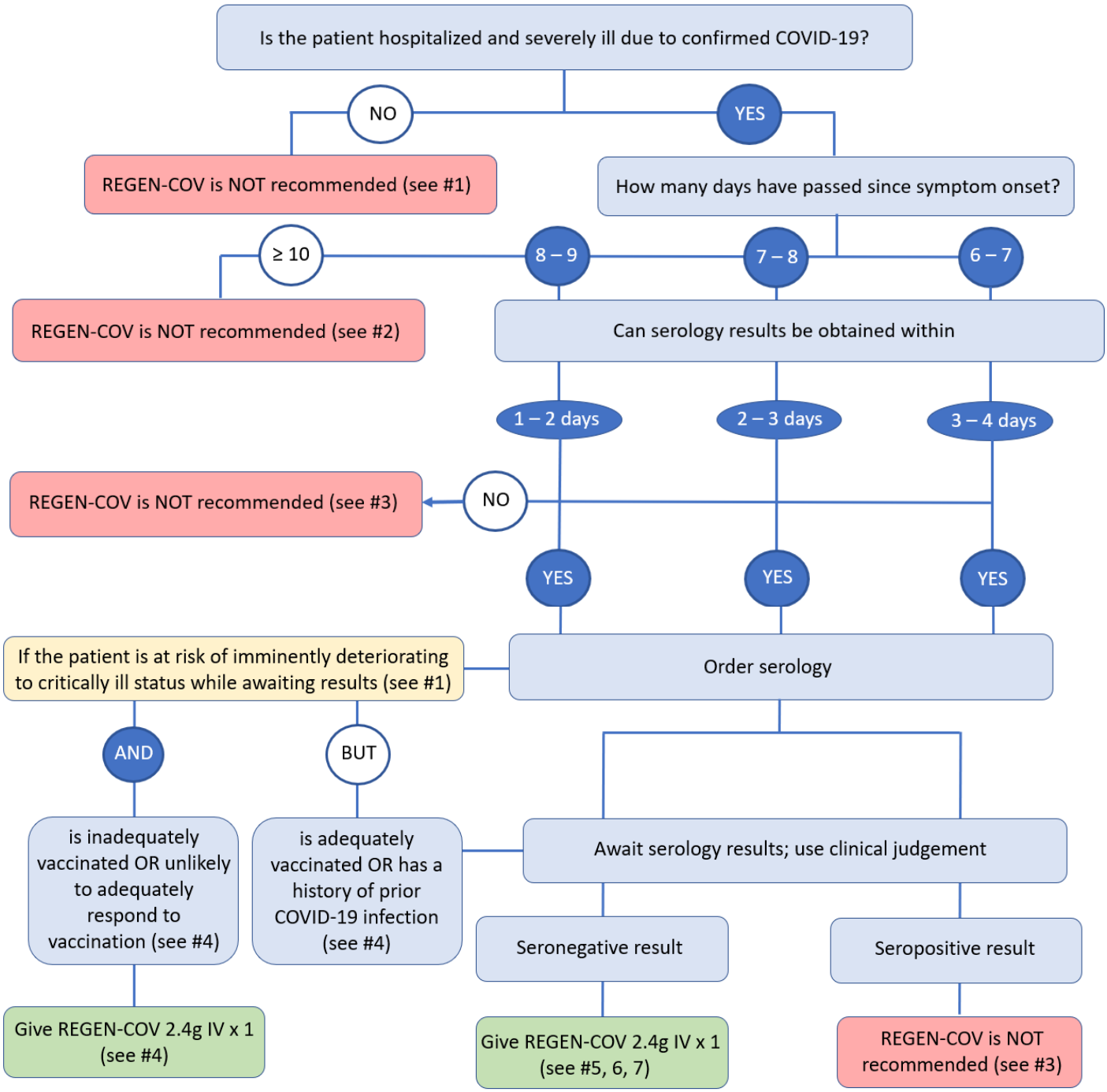
6. Casirivimab and imdevimab for injection. In: COVID-19 vaccines and treatments portal. Ottawa: Health Canada; 2021 (Product monograph; https://covid-vaccine.canada.ca/info/pdf/casirivimab-imdevimab-pm-en.pdf, accessed 16 Nov 2021)
7. https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugsvaccines-treatments/interim-order-import-sale-advertising-drugs.html#a2.8




#1 – Severely ill patients are those who are hospitalized due to symptoms of confirmed COVID-19 and who are receiving low flow supplemental oxygen through nasal prongs, OR receiving hi-flow supplemental oxygen if flow rate ≤ 30 L/min and FiO2 ≤ 0.4 and NOT critically ill (requiring organ support or ICU-level care)
#2 – REGEN-COV should be administered within 10 days of symptom onset
#3 – Absence of anti-spike IgG should be confirmed by serological testing within the 10-day symptom window, irrespective of COVID-19 vaccine status
#4 – Unvaccinated or partially unvaccinated (received 0 or 1 of 2 COVID-19 vaccine doses) OR Unlikely to adequately respond to vaccination despite two COVID-19 vaccine doses due to: bone marrow transplant, solid organ transplant, hematopoietic stem cell transplant in the last 2 years, primary immunodeficiency, OR treatment for an active haematological malignancy OR receiving B-cell depleting (e.g. rituximab, ocrelizumab) within the past year
#5 – Dose REGEN-COV: 2.4g (1.2g casirivimab + 1.2g imdevimab) IV x 1
#6 – Treatment is given in conjunction to current standard of care (e.g. steroids, therapeutic anticoagulation)
#7 – Inform patient of unapproved nature of REGEN-COV therapy under Health Canada's Interim Order and obtain consent