Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Among COVID-19 patients should interferon be used for treatment?

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RECOMMENDATION

We recommend against the use of interferon in the treatment of COVID-19 patients. *(Very low certainty of evidence; Strong recommendation)*

Consensus Issues
Recent review included more participants (close to 6,000) yet, interferon still did not show any clear benefit for all-cause mortality and other critical outcomes. There is a need to emphasize the potential harm and side effects of the drug as well as its high cost.

PREVIOUS RECOMMENDATION

We suggest against the use of interferon in the treatment of hospitalized patients with moderate to critical COVID-19. *(Very low certainty of evidence; Weak recommendation)*

Previous consensus issues
Current evidence shows no significant benefit with using interferon for treating COVID-19 infections. The high cost this drug must be considered.

What's new in this version?

Six (6) new RCTs (Bhushan 2021, Pandit 2021, Ader 2021, Darazam 2021, Khalil 2021, and Rahmani 2020) were included in this update.

Key Findings

Nine (9) published randomized controlled clinical trials (RCTs) (N = 5,957) investigated the efficacy and safety of interferon in the treatment of COVID-19 compared to standard of care and/or placebo. Results showed significant benefit on viral negative conversion among patients given interferon, however, there was inconclusive evidence in terms of the critical outcomes such as all-cause mortality, clinical improvement, need for mechanical ventilation, progression to severe disease, ICU admission, adverse events, and serious adverse events.

Introduction

Interferons are used for treatment and control of multiple sclerosis, viral hepatitis and some hematologic malignancies. Type I interferon (IFN-I) includes interferon alpha and beta.[1] IFN-I response is the first line defense against viral infection. Evasion of interferon response leads to

viral transmission, replication and infection. Interferons modulate the response of the immune system to viruses.[2] An in-vitro study showed that IFN-I reduced viral replication, antigen expression, and viral load in SARs-CoV-2 [3], hence these are under investigation as a potential treatment for individuals with COVID-19.

Review Methods

A systematic search was done from the date of the last search on March 30, 2021 until November 5, 2021. Search was done in Medline, Cochrane Library, and Google scholar using free text, MeSH terms and advanced search using the term coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2, and interferon. Trials found in the COVID-NMA were included. Screening with ongoing trials was done in various trial registries. Medrxiv, chinaxiv, and biorxiv were searched for preprints. RCTs on interferon as treatment for COVID-19 compared to placebo were included. No limits were placed on age, severity and dose. In order to compute for confidence interval, we imputed 1 if a study had no event in the treatment arm.

Results

Characteristics of included studies

Nine (9) published randomized controlled clinical trials (RCTs) (N = 5,957) investigated the effectiveness of interferon among confirmed COVID-19 patients compared to placebo and/or standard of care. All the trials reviewed were also included in the COVID-NMA Living Data.[4-12] Appendix 3 summarizes the characteristics of the included studies.

The severity of the patients included were as follows: mild 1,156 (19.41%), moderate 4,259 (71.4%), moderate to severe 60 (1.01%), and severe 482 (8.09%). Five (5) studies compared interferon beta-1b to standard of care and/or placebo.[4-8] One study compared the effectiveness of interferon beta-1a plus hydroxychloroquine, lopinavir/ritonavir to interferon beta-1b plus hydroxychloroquine, lopinavir/ritonavir and to standard of care hydroxychloroquine, lopinavir/ritonavir.[9] One study compared the effectiveness of interferon beta-1b to standard of care in the treatment of COVID-19 [10], while, two (2) studies compared the effectiveness of PEG-interferon alpha-2b compared to standard of care in the treatment of COVID-19.[11-12] The standard of care included in the studies are hydroxychloroquine, lopinavir/ritonavir, atazanavir/ritonavir, remdesivir, steroids, IVIg, steroids, antibiotics, antipyretics, anticoagulants, and oxygen supplementation depending on the national clinical management guidelines. In three (3) RCTs [4,5,11], 1,078 patients in the IFN arm and 1,144 patients in the control group were given glucocorticoids.

Overall certainty of evidence

The overall certainty of evidence was rated very low due to very serious risk of bias, serious inconsistency, and imprecision in 4 critical outcomes (all-cause mortality, need for mechanical ventilator, clinical improvement, and serious adverse events). The included studies had a very serious risk of bias due to issues on performance bias, detection bias, attrition bias, and reporting bias. Seven out of nine trials were open label trials. The risk of bias summary is shown in Appendix 4. The GRADE evidence summary is in Appendix 5.

Outcomes

Interferon showed significant benefit on one of the important, but not critical outcome, viral negative conversion (RR 1.30, 95% CI 1.14, 1.49; I^2 = 0%; 2 RCTs, 290 participants). However, interferon showed no significant benefit compared to standard of care and/or placebo in all-cause mortality (RR 1.06, 95% CI 0.91, 1.23; I^2 = 48%; 9 RCTs, 5,957 participants), need for mechanical

ventilation (RR 0.97, 95% CI 0.82, 1.14; I^2 = 0%; 4 RCTs, 4,307 participants), clinical improvement (RR 1.02, 95% CI 0.98, 1.06; I^2 = 52%; 6 RCTs, 1,732 participants), progression to severe disease (RR 0.57, 95% CI 0.23, 1.42; 1 RCT, 98 participants), ICU admission (RR 0.77, 95% CI 0.59, 1.00; I^2 = 46%; 2 RCTs, 126 participants), and duration of hospitalization (MD 2.55, 95% CI -0.92 to 6.02; 1 RCT, 81 participants). Results on all cause mortality and clinical improvement also showed borderline heterogeneity.

Subgroup analyses on the effect of interferon on mortality were stratified according to types of interferon used and severity (Appendix 5). Subgroup according to types of interferon used did not show significant benefit across groups, including those given interferon beta-1a (RR 0.91, 95% CI 0.61, 1.36; I^2 = 53%; 6 RCTs, 5,571 participants); those given interferon beta-1b (RR 0.51, 95% CI 0.23, 1.12; I^2 = 0%; 2 RCTs, 96 participants); and those given interferon alpha-2a (RR 2.01, 95% CI 0.36, 11.30; I^2 = 0%; 2 RCTs, 290 participants). Subgroup on interferon beta-1a had borderline heterogeneity (p = 0.06).

Subgroup analysis by severity did not show significant benefit across groups, including those patients belonging to mild to severe (RR 1.12, 95% CI 0.95, 1.33; I^2 = 0%; 3 RCTs, 5,167 participants), moderate (RR 2.10, 95% CI 0.40, 11.14; I^2 = 0%; 2 RCTs, 290 participants), moderate to severe (RR 0.76, 95% CI 0.51, 1.14; 3 RCTs, 254 participants), and severe (RR 0.33, 95% CI 0.07, 1.53; 1 RCT, 66 participants). Results of the moderate to severe subgroup had significant heterogeneity (p = 0.04; I^2 = 68%).

Safety

The rates of adverse events among patients receiving interferon (RR 1.13, 95% CI 0.93, 1.38; I^2 = 53%; p = 0.06) did not differ from those not receiving interferon. There was no significant difference in serious adverse events in interferon (RR 0.91, 95% CI 0.71, 1.18; I^2 = 78%; p = 0.001) compared to standard of care/placebo. Both adverse events and serious adverse events presented with heterogeneity. Adverse events reported were chest pain, asthenia, myalgia, headache, nausea, vomiting, hypersensitivity reaction, cough, decreased oxygen saturation, diarrhea, lymphopenia, and pruritus. Serious adverse events reported included acute kidney injury, nosocomial infection, septic shock, deep vein thrombosis, arrhythmia, respiratory failure, and hepatic failure.

All relevant forest plots for the analyses above are found in Appendix 6.

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
US-NIH Guidelines as of October 27, 2021 [13]	Recommends against the use of interferons for the treatment of patients with severe or critical COVID-19, except in a clinical trial (*Strength of recommendation is AIII*) and states that there are insufficient data to recommend either for or against the use of interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

Australian Guideline on COVID-19 as of November 3, 2021 [14]	Recommends against the use interferons the treatment of COVID-19 except in the context of randomized trials. *(Moderate priority recommendation and will be updated when new evidence becomes available*)
WHO Living Guidelines as of September 24, 2021 [15]	No statement on the use of interferons for the treatment of COVID-19.
Infectious Diseases Society of America (IDSA) as of November 18, 2021 [16]	

Research Gaps

As of November 5, 2021, there are 23 ongoing trials on interferon alpha and interferon beta registered on *clinicaltrials.gov*, EU Clinical Trials Register, and WHO International Clinical Trials Registry Platform (Appendix 9). One of the trials was terminated, two trials are already on Phase 3 and two trials are on Phase 4.

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Appendix 1. Evidence to Decision Table

Table 1. Summary of initial judgements prior to the panel discussion (N = 5)

FACTORS	JUDGEMENT (N = 5)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (4)					
Benefits	Large	Moderate	Small (5)	Uncertain			Interferon showed no significant benefit compared to standard of care and/or placebo in all-cause mortality (RR 1.06, 95% CI 0.91-1.23), need for mechanical ventilation (RR 0.97, 95% CI 0.82-1.14), clinical improvement (RR 1.02 95% CI 0.981.06), progression to severe disease (RR 0.57, 95% CI 0.23-1.42), ICU admission (RR 0.77, 95% CI 0.59-1.00), and duration of hospitalization (MD 2.55, 95% CI -0.92 – 6.02). Interferon showed significant benefit on one of the important, but not critical outcome, viral negative conversion (RR 1.30, 95% CI 1.14-1.49).
Harm	Large (1)	Small (2)	Uncertain (2)				Interferon showed no significant difference in the risk for adverse events (RR 1.13, 95% CI 0.93-1.38) and serious adverse events (RR 0.91, 95% CI 0.71-1.18).
Certainty of Evidence	High	Moderate	Low (2)	Very low (3)			The overall certainty of evidence rated very low due to very serious risk of bias, serious inconsistency and imprecision in 4 critical outcomes.
Balance of effects	Favors drug	Does not favor drug (3)	Uncertain (2)				Interferon showed no potential harm since there is no significant difference in the adverse event and serious adverse event. With the balance favoring benefit in the viral negative conversion.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (5)	Moderate Cost	Negligible cost	Moderate savings	Large savings	Large cost amounting to P19,144.55 to P463,650.00 for the total cost of treatment per patient
Certainty of evidence of required resources	No included studies (5)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (4)	Reduced (1)	Probably no impact	Increased			
Acceptability	Uncertain (3)	No (2)	Yes				
Feasibility	Uncertain (2)	No (2)	Yes (1)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Interferon AND randomized	10/31/2021 3:20PM	188	12
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND MeSH descriptor: [Interferons] explode all trees	10/31/2021 5:05PM	60	17
COVID-NMA Initiative	Interferon	10/30/2021 4:30PM	18	8
Google Scholar	allintitle: interferon AND "COVID 19" custom range: 2020-2021	11/5/2021 4:37PM	117	8
ClinicalTrials.gov	COVID-19 COVID-19 Pneumonia, Investigational Trials, Interferon	11/5/2021 8:30PM	44	16
Chinese Clinical Trial Registry	Advanced: COVID, randomly sampling, interferon	11/5/2021 9:40PM	0	0
EU Clinical Trials Register	COVID AND Interferon	11/5/2021 9:44PM	7	1
Republic of Korea - Clinical Research Information Service	COVID AND Interferon	11/5/2021 9:46PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	COVID AND Interferon	11/5/2021 9:47PM	0	0
CenterWatch	COVID AND Interferon	11/5/2021 9:48PM	0	0

WHO International Clinical Trials Registry Platform	COVID AND Interferon (Filter 01/01/2021 to 11/05/2021)	11/5/2021 9:54PM	53	14
chinaxiv.org	COVID Interferon	11/5/2021 10:41PM	0	0
Medrxiv.org	COVID AND Interferon AND Randomized Filter: April 10-November 11	11/5/2021 10:47PM	180	1
Biorxiv.org	COVID AND Interferon AND Randomized Filter: April 10-November 11	11/5/2021 11:21PM	251	0

Appendix 3: Characteristics of Included Studies

Title/Author	Study design	Country	Population	Intervention Group(s)	Control	Outcomes
Pan 2020 WHO Solidarity Trial Consortium N = 4,100	Adaptive Open-label RCT	30 countries Albania, Austria, Belgium, Finland, France, Ireland, Italy, Lithuania, Luxembourg, North Macedonia, Norway, Spain, Switzerland, Argentina, Brazil, Colombia, Honduras, Peru, Egypt, India, Indonesia, Kuwait, Lebanon, Malaysia, Pakistan, Philippines, Saudi Arabia, South Africa	Hospitalized COVID-19 patients Mild to severe	Interferon β-1a 44µg 3 doses subcutaneous over a period of 6 days OR 10µg intravenously daily for 6 days	Standard care	All-cause mortality Need for mechanical ventilation
Davoudi-Monferad 2020 N = 81	Open-label RCT	Iran	Confirmed covid-19 patients, >50% bilateral opacities on CT scan, <90% O2, hypotension, renal failure secondary to COVID-19, neurologic disorder 3 secondary to COVID-19, Thrombocytopenia Moderate to severe	Interferon β-1a 44µg/ml subcutaneously 3x a week for 2 consecutive weeks	Standard of care	All- cause mortality Clinical Improvement Time to clinical improvement Duration of hospitalization Duration of ICU stay Duration of mechanical ventilation Serious Adverse Events Adverse Events
Monk 2021 UK N = 98	Randomized, double-blind placebo-controlled, phase 2	UK	Confirmed COVID-19 patients Mild to severe	SNG001 (recombinant Interferon β-1a) 6 MIU via nebulizer once daily for up to 14 days	Placebo	All- cause mortality Clinical Improvement Progression to severe COVID-19 Serious Adverse Events Adverse Events
New Added Studies (As of November 5, 2021)						
Ader 2021 DisCoVeRy N = 293	Open-label Adaptive RCT	France	Hospitalized confirmed COVID-19 patients, pulmonary rales or crackels, O2 sat ≤94% or requiring supplemental oxygen Moderate to severe	IFN β-1a 44 µg subcutaneously on days 1, 3 and 6 PLUS Lopinavir/ritonavir PLUS standard of care	Standard of care	Clinical improvement Day 15 Clinical improvement Day 29 Time to clinical improvement All-cause mortality Day 29 Adverse events Serious Adverse events
Kalil 2021 N = 969	Randomized, double-blind placebo-controlled	Japan, Mexico, Singapore, South Korea, USA	Hospitalized confirmed COVID-19 patients one of the following criteria of lower respiratory tract infection: radiographic infiltrates on imaging, SpO2 ≤94%, or requiring O2 supplementation Mild to severe	Interferon beta-1a 44 µg 4 doses PLUS Remdesivir	Placebo PLUS Remdesivir	Time to clinical recovery day 28 Clinical improvement Time to clinical improvement Duration of supplemental oxygen Duration of hospitalization All-cause mortality Adverse event Serious adverse event

Darazam 2021 COVIFERON N = 60	Open-label RCT	Iran	Confirmed COVID-19 patients with RTPCR and CT scan, SpO2 ≤93% OR RR ≥24 on ambient air and acute symptoms (≤14 days) Moderate to severe	Experimental 1: IFN β-1a 44 µg subcutaneous day 1, 3 and 6 PLUS Hydroxychloroquine + Lopinavir/ritonavir Experimental 2: IFN β-1b subcutaneous 0.25mg (8 MIU) PLUS Hydroxychloroquine + Lopinavir/ritonavir	Hydroxychloroquine+Lopinavir/Ritonavir	Time to clinical improvement All-cause mortality day 21 Need for mechanical ventilation Adverse event Serious adverse event
Rahmani 2020	Open-label RCT	Iran	Confirmed COVID-19 patient with clinical signs/symptoms of pneumonia, SpO2 ≤93% or Pao2/FiO2 <300 SpO2/FiO2 < 315 and lung involvement in chest imaging Severe	IFN β-1b 250mcg subcutaneously every other day for two consecutive weeks	Standard of care	Time to clinical improvement ICU admission Need for mechanical ventilation Duration of hospitalization All-cause mortality
Bhushan 2021 N = 250	Open-label RCT	India	Confirmed COVID-19 patient, Moderate SpO2 90-94% RR ≥24, Pneumonia without signs of severe pneumonia Moderate	PEG IFN α2b 1µg/kg, Subcutaneous, single dose PLUS standard of care	Standard of care	Clinical improvement Viral negative conversion Need for supplemental oxygen Need for mechanical ventilation Time to resolution of symptoms Adverse events
Pandit 2021 N= 40	Open-label RCT (Phase II)	India	Confirmed COVID-19 patient, Moderate SpO2 90-94% RR15-30, Pneumonia without signs of severe pneumonia CRP < 16mg/L, IL-6 <100 pg/ml, D-dimer < 2 µg/ml, interferon γ, ferritin, TNF-α, IL-1β> upper limit of normal Moderate	PEG IFN α2b 1µg/kg, Subcutaneous, single dose PLUS standard of care	Standard of care	Clinical improvement Adverse events Need for supplemental oxygen Need for mechanical ventilation Duration of hospitalization Viral negative conversion

Appendix 4. Study Appraisal

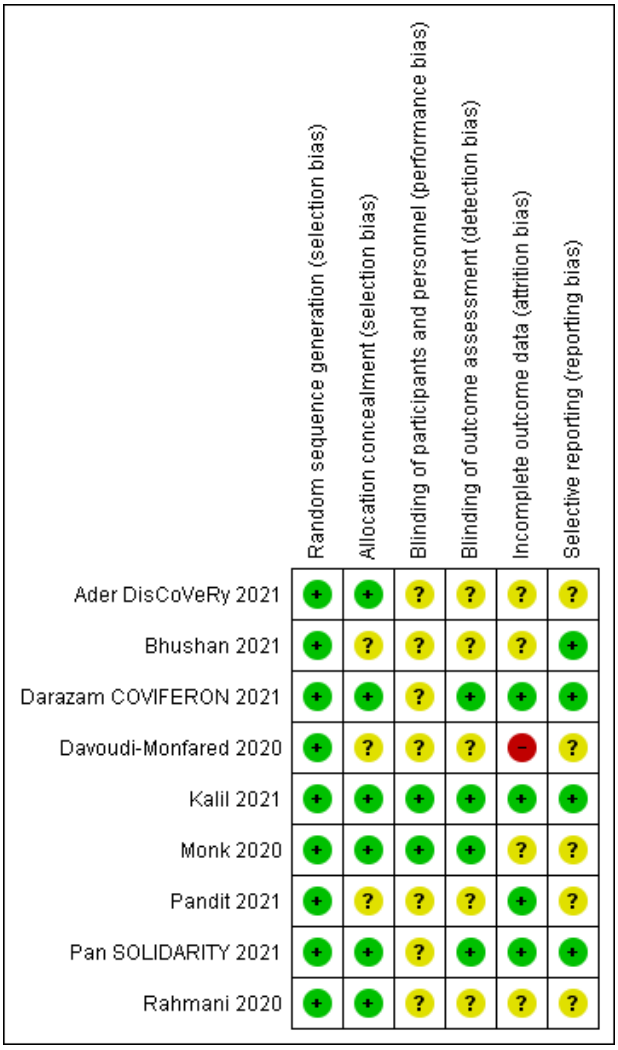

Figure 1. Risk of bias summary table

Appendix 5: GRADE Evidence Profile

Author(s): Katherine O. Relato

Question: Interferon compared to Standard of Care for COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
9	randomised trials	very serious[a,b]	not serious	not serious	serious[c]	none	306/2985 (10.3%)	282/2972 (9.5%)	**RR 1.06** (0.91 to 1.23)	**6 more per 1,000** (from 9 fewer to 22 more)	⨁◯◯◯ VERY LOW	CRITICAL
Need for mechanical ventilation												
4	randomised trials	very serious[a,b]	not serious	not serious	serious[c]	none	240/2165 (11.1%)	240/2142 (11.2%)	**RR 0.97** (0.82 to 1.14)	**3 fewer per 1,000** (from 20 fewer to 16 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinical Improvement												
6	randomised trials	very serious[a,b]	serious[d]	not serious	serious[c]	none	693/862 (80.4%)	683/870 (78.5%)	**RR 1.02** (0.98 to 1.06)	**16 more per 1,000** (from 16 fewer to 47 more)	⨁◯◯◯ VERY LOW	CRITICAL
Progression to severe disease												
1	randomised trials	serious[b]	not serious	not serious	serious[c,e]	none	6/48 (12.5%)	11/50 (22.0%)	**RR 0.57** (0.23 to 1.42)	**95 fewer per 1,000** (from 169 fewer to 92 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events												
5	randomised trials	very serious[a,b]	serious[f]	not serious	serious[c]	none	373/862 (43.3%)	315/869 (36.2%)	**RR 1.13** (0.93 to 1.38)	**47 more per 1,000** (from 25 fewer to 138 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events												
5	randomised trials	very serious[a,b]	serious[g]	not serious	serious[c]	none	236/762 (31.0%)	234/739 (31.7%)	**RR 0.91** (0.71 to 1.18)	**28 fewer per 1,000** (from 92 fewer to 57 more)	⨁◯◯◯ VERY LOW	CRITICAL
Duration of hospitalization												
1	randomised trials	very serious[a,b]	not serious	not serious	serious[c]	none	42	39	-	MD **2.55 days higher** (0.92 lower to 6.02 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Viral negative conversion												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	119/140 (85.0%)	98/150 (65.3%)	**RR 1.30** (1.14 to 1.49)	**196 more per 1,000** (from 91 more to 320 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
ICU admission												
2	randomised trials	serious[a]	not serious	not serious	serious[c,e]	none	43/73 (58.9%)	38/53 (71.7%)	**RR 0.77** (0.59 to 1.00)	**165 fewer per 1,000** (from 294 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. performance and detection bias
b. attrition and reporting bias

c. wide confidence interval with possibility for benefit and harm
d. I2=52%
e. small number of events does not reach optimal information size
f. I2=53%
g. I2=78%

Appendix 6. Forest Plots

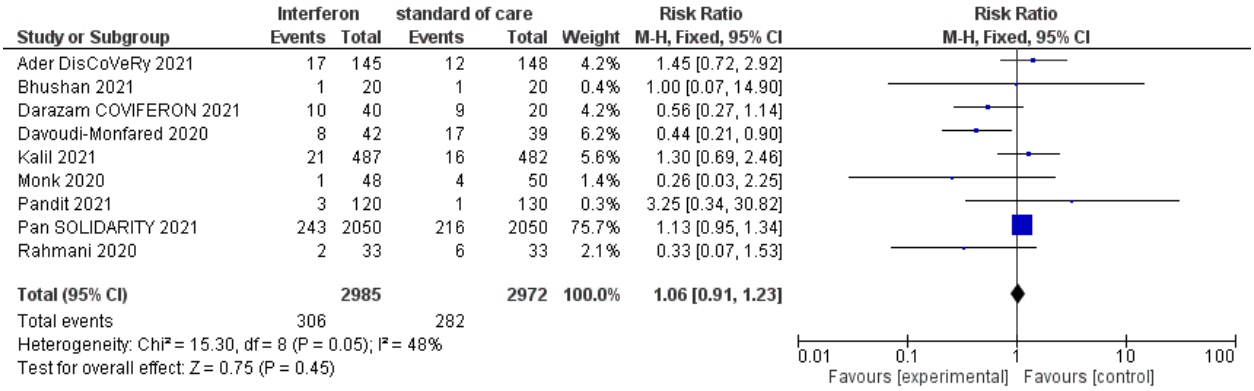

Figure 1.1. All-cause mortality

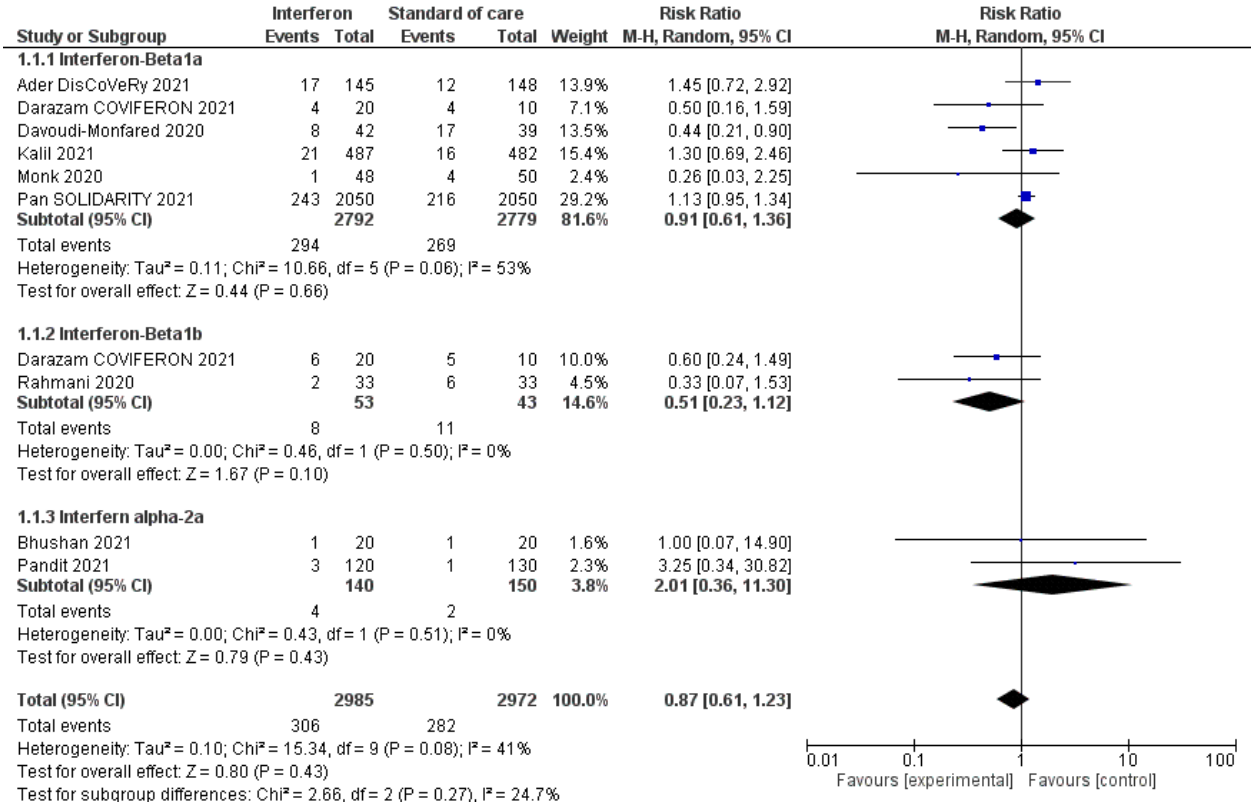

Figure 1.2 All-cause mortality subgroup based on types of interferon

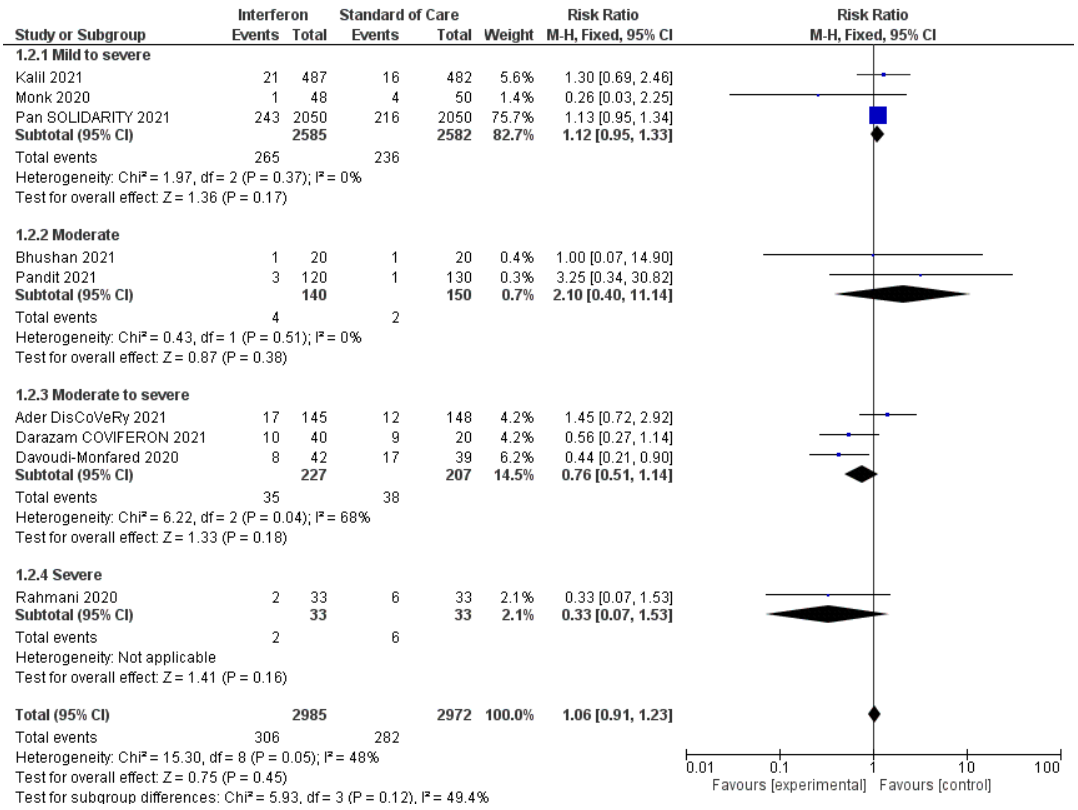

Figure 1.3 All-cause mortality subgroup based on severity

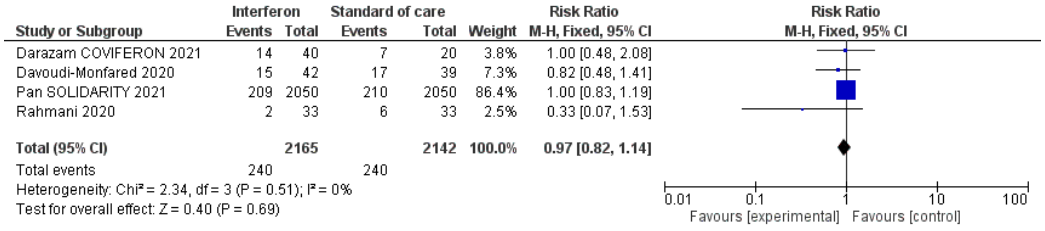

Figure 2. Need for mechanical ventilation

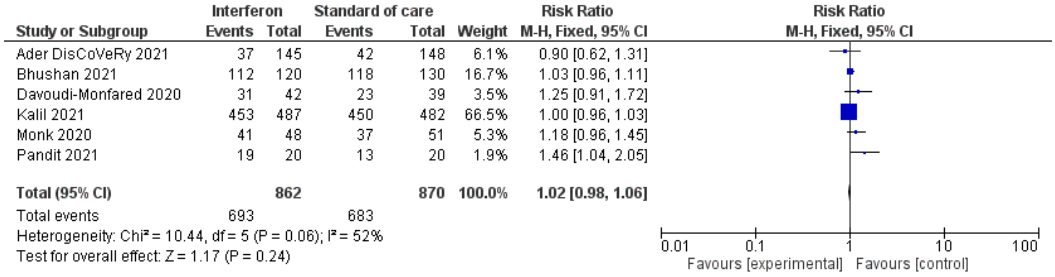

Figure 3. Clinical Improvement

Figure 4. ICU admission

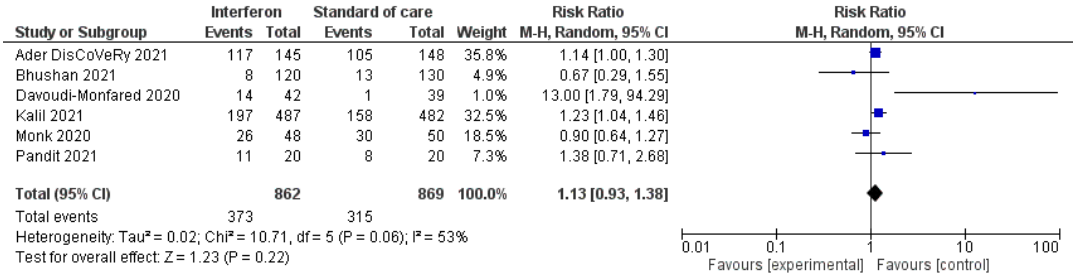

Figure 5. Adverse events

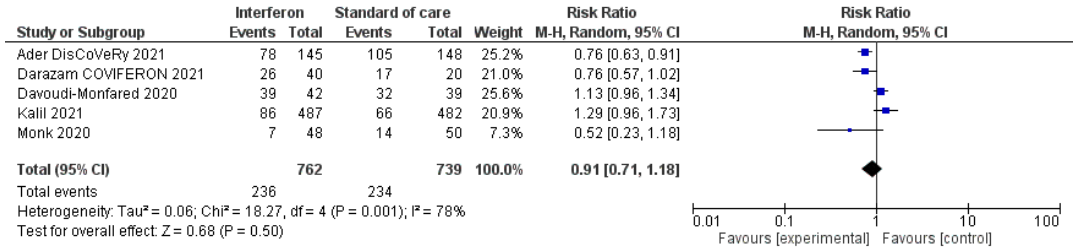

Figure 6. Serious Adverse Events

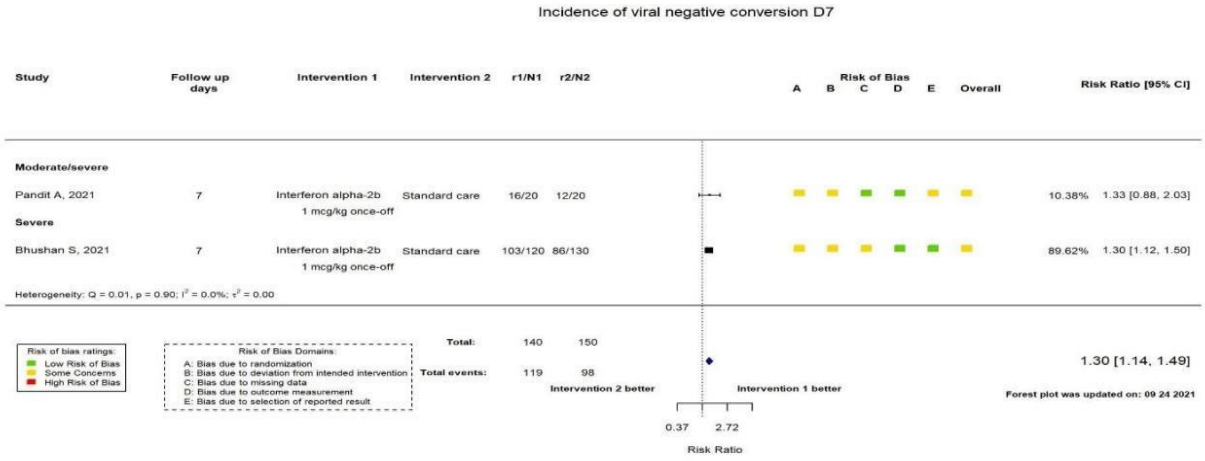

Figure 7. Viral negative conversion

Appendix 7. Pooled Results of Trials

Outcome	Pooled/ Relative Risk	95% CI	Certainty of evidence (GRADE)
All-cause mortality (9 RCTs, N = 5,957)	1.06	0.91 to 1.23	Very Low
Need for mechanical ventilation (4 RCTs, N = 4,307)	0.97	0.82 to 1.14	Very Low
Clinical improvement (6 RCTs, N = 1,732)	1.02	0.98 to 1.06	Very Low
Progression to severe disease (1 RCT, N = 98)	0.57	0.23 to 1.42	Low
Serious adverse event (5 RCTs, N = 1,501)	0.91	0.71 to 1.18	Very Low
Adverse events (6 RCTs, N = 1,731)	1.13	0.93 to 1.38	Very Low
Duration of hospitalization (1 RCT, N = 81)	MD= 2.55	-0.92 to 6.02	Very Low
ICU admission (2 RCTs, N = 126)	0.77	0.59 to 1.00	Low
Viral negative conversion (2 RCTs, N = 290)	1.30	1.14 to 1.49	Moderate

Appendix 8. Subgroup Analysis

	Pooled Relative Risk	95% CI	Certainty of Evidence
By type of Interferon			
Interferon beta-1a (6 RCTs, n = 5,581)	0.91	0.61 to 1.36	Very Low
Interferon beta-1b (2 RCTs, n = 106)	0.51	0.23 to 1.12	Low
Interferon alpha-2a (2 RCTs, n = 290)	2.01	0.36 to 11.30	Low
By severity			
Mild to severe (3 RCTs, n = 5,167)	1.12	0.95 to 1.33	Low
Moderate (2 RCTs, n = 290)	2.10	0.40 to 11.14	Low
Moderate to severe (3 RCTs, n = 254)	0.76	0.51 to 1.14	Very Low
Severe (1 RCT, n = 66)	0.33	0.07 to 1.53	Low

Appendix 9. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. IFN-beta 1b and Remdesivir for COVID19 Recruiting Phase 2	≥18 years hospitalized for confirmed SARS-CoV-2 infection with one of the following criteria: age 65 years or above, radiological evidence of pneumonia, oxygen desaturation <94% on room air, comorbidity including hypertension, diabetes, cardiovascular diseases, chronic obstructive lung disease, chronic liver diseases, chronic kidney diseases, malignancy, haematological diseases, rheumatological diseases, immunocompromised hosts and obesity (BMI > 30) (n=100)	Experimental: Interferon- beta 1b (16 million IU) and remdesivir 200mg IV day 1 then 100mg daily day 2-5 Control: Remdesivir 200mg IV day 1 then 100mg daily day 2-5	Primary: Clinical improvement (30 day)	Randomized, parallel, open label
2. Dual Therapy with Interferon Beta-1b and Clofazimine for COVID-19 Recruiting Phase 2	18 years or above hospitalized for virologic confirmed SARS-CoV-2 infection (n=81)	Experimental 1: Interferon beta-1b (16 million IU) SC day 1-3 and Clofazamine PLUS standard of care Experimental 2: Clofazamine PLUS standard of care Control: Standard of care	Primary: Clinical alleviation of symptoms (7 days)	Randomized parallel, open label
3. Clinical Study for the Treatment with Interferon-ß-1a (IFNß-1a) of COVID-19 Patients (INTERCOP) Terminated	Hospitalized with confirmed swab RT-PCR detection of SARS-CoV-2, X-ray and/or CT diagnosed pneumonia, Age >=18 years, Clinical status defined as 3, 4 or 5 on the 7-point ordinal scale (n=56)	Experimental: Interferon beta-1a SC 12 million IU 3 times a week at least 48 hrs apart for 2 weeks Control: Standard of care	Primary: Time to negative conversion of SARS-CoV-2 nasopharyngeal swab (day 29)	Randomized, parallel, open label
4. IFN Beta-1b and Ribavirin for Covid-19 Recruiting Phase 2	≥18 years hospitalized for confirmed SARS-CoV-2 infection. (n=96)	Experimental: Interferon beta-1b 16 million IU and Ribavirin PLUS standard of care Control: Standard of care	Primary: Clinical symptoms alleviation (7 days)	Randomized Parallel, open label
5. Inhaled Interferon α2b for the Treatment of Coronavirus Disease 19 (COVID-19) (IN2COVID) Recruiting Phase 2	Male subjects aged 18-50 years;In good state of health, determined by medical history, physical exam, and normal Active SARS-CoV-2 infection demonstrated by positive polymerase chain reaction (PCR) ≤ 5 days at enrollment; Symptomatic of mild or moderate COVID-19 for ≤ 5 days at enrollment (n=168)	Experimental 1a: Nebulized Interferon alpha 2b 2.5 million IU every 12 hours during 10 days Experimental 1b: Nebulized Interferon alpha 2b 5 million IU every 12 hours during 10 days Control Part 1: Placebo Experimental 2: nebulized Interferon alpha 2b 5 million IU every 12 hours for 10 days Control Part 2: Placebo	Primary: Treatment-emergent adverse events in healthy subjects [Time Frame: At the end of Phase 1 (11 days) Change in perception of health status measured by EQ VAS in COVID-19 patients (28 days)	Randomized, parallel, open label
6. Interferon Beta 1a in Hospitalized COVID-19 Patients (IB1aIC)	Age ≥ 50, COVID-19 Confirmed Cases, Tympanic Temperature of ≥37.5 AND at least one of the following: Cough, Sputum	Experimental: Interferon-β 1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine	Primary: Time to clinical improvement (14 days)	Randomized, parallel, double-blind,

Enrolling by invitation Phase 4	production, nasal discharge, myalgia, headache or fatigue) on admission, Time of onset of the symptoms should be acute (Days ≤ 10), SpO2 ≤ 88%, Respiratory Rate ≥ 24 (n=40)	Control: Lopinavir / Ritonavir + Single Dose of HydroxychloroquinePlacebo		placebo-controlled
7. Trial of Inhaled Anti-viral (SNG001) for SARS-CoV-2 (COVID-19) Infection Active, not recruiting Phase 2	A. Hospital setting: positive virus test for SARS-CoV-2, ≥18 years of age, admitted to hospital due to the severity of their COVID 19 disease, B. Home setting: positive virus test for SARS-CoV-2, ≥50 years of age at the time of consent, non-hospitalized patients from high-risk groups, defined as ≥65-years of age, or ≥50 years of age and with any risk factors (n=820)	Experimental: SNG001(interferon beta) inhalation using the I-neb device. Control: Placebo	Primary: Ordinal Scale for Clinical Improvement	Randomized, parallel, double-blind placebo-controlled
8. Pegylated Interferon - α2b With SARSCoV- 2 (COVID-19) Active not recruiting Phase 2	Male or non-pregnant females, ≥18 years of age at the time of enrolment. Has laboratory-confirmed SARS-CoV-2 infection, with SpO2 > 93% and respiratory rate <30 breaths/min,illness of any duration, and at least one of the following: Radiographic infiltrates by imaging, clinical assessment (evidence of rales/crackles or other clinical symptoms on exam) (n=40)	Experimental: Pegylated Interferon-α2b 1 mcg/kg on day 1 and day 8 after safety evaluations PLUS standard of care Control: Standard of care	Primary: Change in Clinical status of subject on a 7-point	Randomized parallel, open-label
9. Efficacy and Safety of IFN-α2β in the Treatment of Novel Coronavirus Patients Not yet recruiting Early Phase 1	Age ≥ 18 years; Clinically diagnosed patients with new type of coronavirus pneumonia, including: in accordance with the criteria for suspected cases, have one of the following etiology evidence: RT-PCR, Sequencing of viral genes in respiratory specimens or blood specimens, highly homologous to known new coronavirus. The time interval between the onset of symptoms and random enrollment is within 7 days (n=328)	Experimental: Recombinant human interferon α1β 10ug Bid was administered by nebulization for 10 days plus standard of care Control: Standard of care	Primary: Incidence of side effects	Randomized parallel, open label
10. Human Intravenous Interferon Beta-Ia Safety and Preliminary Efficacy in Hospitalized Subjects with CoronavirUS (HIBISCUS) Recruiting Phase 2	Age ≥18 years, Positive SARS-CoV-2 test by PCR, Admission to hospital with respiratory symptoms of COVID-19 requiring hospital care and oxygen supplementation (≤ 8L/min), Symptom onset no more than 7 days prior to hospital arrival (n=140)	Experimental: IFN beta-1a 10 µg as an IV bolus for 6 days while hospitalised Control: Dexamethasone	Clinical status at Day 14 (first day of study drug is Day 1) as measured by WHO 9-point ordinal scale	Randomized, parallel, double-blind
11. Treatment of COVID-19 by Nebulization of Inteferon Beta 1b Efficiency and Safety Study (COV-NI) Recruiting	≥ 18 years old, confirmed SARS-CoV-2 infection as determined by PCR < 96 h (at initial diagnosis or persistent carriage <96 h), Hospitalized patient with COVID-19 requiring oxygen therapy, And targeting in phase B: under oxygen therapy such as nasal cannula/mask or non-	Experimental: Inhaled interferon (9.6 MUI x2/d for 48 hours, then 9.6 MUI x1/d for 8 to 16 days or discharge), in addition to standard care. Control: Placebo	Oxygen requirement score at day 0 Oxygen requirement score at day 15 Variation oxygen requirement score	Randomized, double-blind

Phase 2	invasive ventilation with paO2/FiO2 > 200 mmHg, hospitalized for less than 7 days, patients with symptoms for less than 10 days or RT-PCR (<96h) with Cycle Threshold < 25		between day 0 and day15	
12. Public Health Emergency: SOLIDARITY TRIAL Philippines Active not recruiting	Age ≥18 hospitalized with: probable or confirmed COVID-19 regardless of severity, Not already receiving any of the study drugs, without known allergy or contraindications to any of the study drugs (in the view of the physician responsible for their care), and without anticipated transfer within 72 hours to a non-study hospital.	Experimental 1: Remdesivir with SoC Experimental 2: Hydroxychloroquine with Soc Experimental 3: Lopinavir/Ritonavir with SoC Experimental 4: Acalabrutinib with SoC Experimental 5: Interferon beta-1a with SoC Control: Standard of care	Primary: All-cause mortality	Randomized parallel, adaptive open label
13. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP) Recruiting Phase 4	Adult patient admitted to an ICU for severe CAP within 48 hours of hospital admission with: symptoms or signs or both that are consistent with lower respiratory tract infection AND radiological evidence of new onset consolidation Up to 48 hours after ICU admission, receiving organ support with one or more of: Non-invasive or Invasive ventilatory support; receiving infusion of vasopressor or inotropes or both	Experimental 1: Interferon B1a 10 ug IV bolus once daily for 6 days or until ICU discharge Others: Hydrocortisone, Ceftriaxone, Moxifloxacin/Levofloxacin, Piperacillin-tazobactam, Ceftaroline, Amoxicillin-clavulanate, Macrolide, Oseltamivir, Lopinavir/ritonavir, Hydroxychloroquine, anakinra, tocilizumab, sarilumab, vitamin c, therapeutic anticoagulation	Primary: All-cause mortality Days alive and not receiving organ support in ICU	Randomized Factorial open label
14. Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial (CATCO) Recruiting Phase 2	≥ 18 years of age, laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or Hospitalized at a participating centre (n= 440)	Experimental 1: Interferon Beta 1a plus standard supportive care Experimental 2: Remdesivir plus standard supportive care Control: Standard supportive care	Primary: all-cause mortality	Randomized, parallel, open label
15. Study to Assess Efficacy and Safety of Inhaled Interferon-β Therapy for COVID-19 (SPRINTER) Recruiting Phase 3	Admitted to hospital due to the severity of their COVID-19, Positive virus test for SARS-CoV-2, Require oxygen therapy via nasal prongs or mask (WHO OSCI score of 4)	Experimental: inhaled interferon B (SNG001) once daily Control: Placebo	Primary: Time to hospital discharge Time to recovery	Randomized, Parallel, Placebo controlled, double blind
15. World Health Organization (WHO) COVID-19 Solidarity Trial for COVID-19 Treatments (SOLIDARITY) Not yet recruiting Phase 3	Consenting adults (age ≥18) hospitalized with definite COVID-19	Experimental 1: Remdesivir Experimental 2: Acalabrutinib Experimental 3: Interferon B1a IV 10 ug once daily for 6 days if oxygen dependent or subcutaneously at 44 ug Day 1, Day 3, and Day 6 Control: Standard of Care	Primary: all-cause mortality	Randomized parallel open label
16. Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease	Symptomatic and laboratory-confirmed diagnosis of COVID-19, ≥18 years old, high risk: either age ≥70 or one of the following: male; obesity (BMI ≥30); chronic	Experimental 1: Colchicine Experimental 2: ASA Experimental 3: Rivaroxaban Experimental 4: Interferon Beta 0.25mg days 1, 3, 5, 7	Primary: Outpatients: Hospital Admission or Death Inpatients: Invasive mechanical	Randomized, parallel, open-label

2019 (COVID-19) Trial (ACTCOVID19) Recruiting Phase 3	cardiovascular, respiratory or renal disease; active cancer; diabetes; Within 7 days (ideally 72 hours) of diagnosis, or worsening clinically	Control: Standard of care	ventilation or mortality	
17. Efficacy and safety of Interferon beta-1-a in mild to moderate COVID-19 Recruiting	COVID-19, based on reverse transcriptase-polymerase chain reaction (rt-PCR), patients with mild to moderate COVID-19 within 48 hours of the onset of the symptoms	Experimental: Interferon B-a 12 million units SC very other day for 3 doses plus acetaminophen and antihistamine Control: Acetaminophen and antihistamine	Primary: BNody temp, DBP, level O2 saturation, PR, RR SBP	Randomized, Open label, parallel
18 Evaluation of the effect of interferon beta-1b in the treatment of COVID-19 Recruiting	Individuals over 18 years of age whose covid-19 disease has been confirmed by PCR test and clinically severely ill, o2sat below 90% despite receiving oxygen, severe bilateral pulmonary involvement	Experimental: Hydroxychloroquine and Kelatra with interferon beta-one B (at a dose of 250 micrograms or 8 million subcutaneously every other day Control: Hydroxychloroquine and kelatra	Primary: Changes in liver enzyme, oxygen saturation, respiratory rate, duration of hospitalization, LDH levels, Moratlity rate	Randomized, open label, parallel
19. Using interferon to treat COVID-19 Recruiting	Adult over 18 years, Clinical diagnosis of COVID-19	Experimental 1: Interferon beta plus standard of care Experimental 2: Interferon alpha plus standard of care Control: Standard of care plus placebo	Primary: Blood gas level, body temperature, respiratory rate, FiO2	Randomized, placebo controlled, double-blind
20. Efficacy evaluation of inhalation therapy (nasal spray) of Interferon Beta-1a in hospitalized Covid-19 patients Recruiting	Patients who have Covid-19 based on the CT-scan or RT-PCR findings, Hospitalized patients, age between 20-65	Experimental: Interferon B1a nasal spray every 6 hours for 7 days and standard of care Control: Placebo	Primary: Viral negative conversion	Randomized, double blind placebo controlled
21. Investigating the efficacy and safety of Interferon Beta1a nasal spray in controlling the symptoms of patients with COVID-19 Recruiting	18 years old or more, clinical symptoms (dry cough, shortness of breath, fever) confirm COVID-19; confirmed diagnosis of COVID-19, less than 7 days have passed since the onset of symptoms.	Experimental: Interferon Beta 1a nasal spray 1 puff in each nostril every 6 hours, for 14 days Control: Standard of care	Primary: Clinical improvement	Randomized, open label, parallel
22. Interferon beta 1b in COVID-19 Recruiting	All adult patients with highly suspected or confirmed COVID-19 who are candidate for hospitalization and starting therapeutic regimen with lopinavir/ritonavir and hydroxychloroquine	Experimental: Hydroxychloroquine, lopinavir/ritonavir and interferon beta 1b Control: Lopinavir/ritonavir hydroxychloroquine	Primary: Clinical improvement	Randomized, open label parallel
23. Efficacy of dexamethasone, IV-IG and Interferone beta for treatment of patients with severe COVID-19 Recruiting	Age 18-70 years Sever COVID19 disease with the following criteria: SPpO2 below 90% and respiratory rate higher 24 per minute; Involvement of more that 50% of lung in CT-scan	Experimental: IVIg, Dexamethasona and Interferone beta Control: Standard of care	Primary: Oxygen improvement	Randomized, open label, parallel