Management of thrombotic risk in ICU patients during the COVID-19 epidemic [Version 10 (21 May 2020)]

The problem
COVID-19 appears to provoke a hyper-inflammatory and pro-thrombotic state in many but not all patients. One observable manifestation is the frequent finding of hyper-fibrinogenaemia and very high levels of D-dimers. There is a suspicion that one of the reasons we are seeing progressive lung and renal failure in some patients is due to microvascular thrombosis (as opposed to venous thrombo-embolism, which also occurs in up to 40% of patients in some series). DIC criteria (low platelet count + high INR + low fibrinogen + elevated D-dimers) are not met in most cases, suggesting that the thrombosis and hyperfibrinolysis represent a localised microvascular imbalance of haemostasis. Hypertriglyceridaemia, may also be a feature of the hyperinflammatory syndrome and a co-factor in thrombosis. Furthermore, we have seen dramatic heparin resistance, especially in the context of extracorporeal circuits, which chimes with the clinical observation of an usually high incidence of intravascular (predominantly venous) thrombosis and massive / sub-massive pulmonary emboli occurring in patients on standard doses of pharmacological prophylaxis.

The proposed solution
Increased doses of subcutaneous Dalteparin / Unfractionated Heparin (UFH) in placed of routine VTE doses based upon weight, renal function and D-dimer levels.
For emerging evidence see: https://www.ncbi.nlm.nih.gov/pubmed/32387623 and https://www.ncbi.nlm.nih.gov/pubmed/32220112

ON ADMISSION TO ICU

1. INCLUSION CRITERIA
    a. COVID-19 hyper-inflammatory syndrome suspected or confirmed
    [Definition = classic history /classic CXR / swab or sputum +ve / ***normal*** WBC + neutrophil count + lymphopaenia / ***raised:*** CRP + fibrinogen + D-dimer + ferritin + LDH]
2. EXCLUSION CRITERIA for using the proposed dosing table:
    a. Platelet count <50 x 10^9/L
    b. Fibrinogen < 2.0g/L
    c. Anticoagulant drug naïve standard clotting time ratio(s) >2.0 [aPTTr and/or INR (PT)]
    d. If a patient has any acute / active bleed - defined as (see also suggest intervention plan IF acute bleeding occurs whilst on anticoagulants):
        i. otherwise unexplained drop in [Hb] ≥20g/L in ≤24 hours ***AND / OR***
        ii. otherwise unexplained haemodynamic instability ***AND / OR***
        iii. obvious macroscopic haemorrhage e.g. frank blood via nose, mouth, nasogastric tube or per rectum
    e. **If the patient has a suspected OR proven arterial OR venous thrombosis THEN USE** the dosing chart as for patients with D-dimer >3000ng/ml

    If any of the exclusion criteria are present – please discuss with the Haematology team urgently to individualise the anticoagulant plan
3. Estimate **ACTUAL BODY WEIGHT; IF <50 OR >150kg** discuss dosing with Haematology team
4. Review most recent eGFR and establish if ≥ ***OR*** <30 *&/OR* on Renal Replacement Therapy (RRT) [if on RRT, eGFR is meaningless]
    If eGFR ≥30 ml/min/1.73m^2 ***USE*** Dalteparin
    If eGFR <30 ml/min/1.73m^2 ***USE*** Unfractionated Heparin (UFH)
5. Review ***THE MOST RECENT*** D-dimer level (taking the trend into account, if available) to determine the thrombosis risk category:
    If D-dimer <1000 ng/ml *THEN* enhanced thromboprophylaxis (Green column)
    If D-dimer 1000-3000 ng/ml *THEN* escalated thromboprophylaxis (Orange column)
    If D-dimer >3000 ng/ml *THEN* therapeutic anticoagulation (Red column)
    NOTE: D-dimers are renally cleared therefore accumulate with renal dysfunction AND are partially cleared by RRT. It is reasonable to view all COVID-19 patients with acute progressive AKI as being likely to benefit from full anticoagulation i.e. treat as being in the **RED** category.
    If uncertain how to interpret D-dimer levels please seek expert advice.

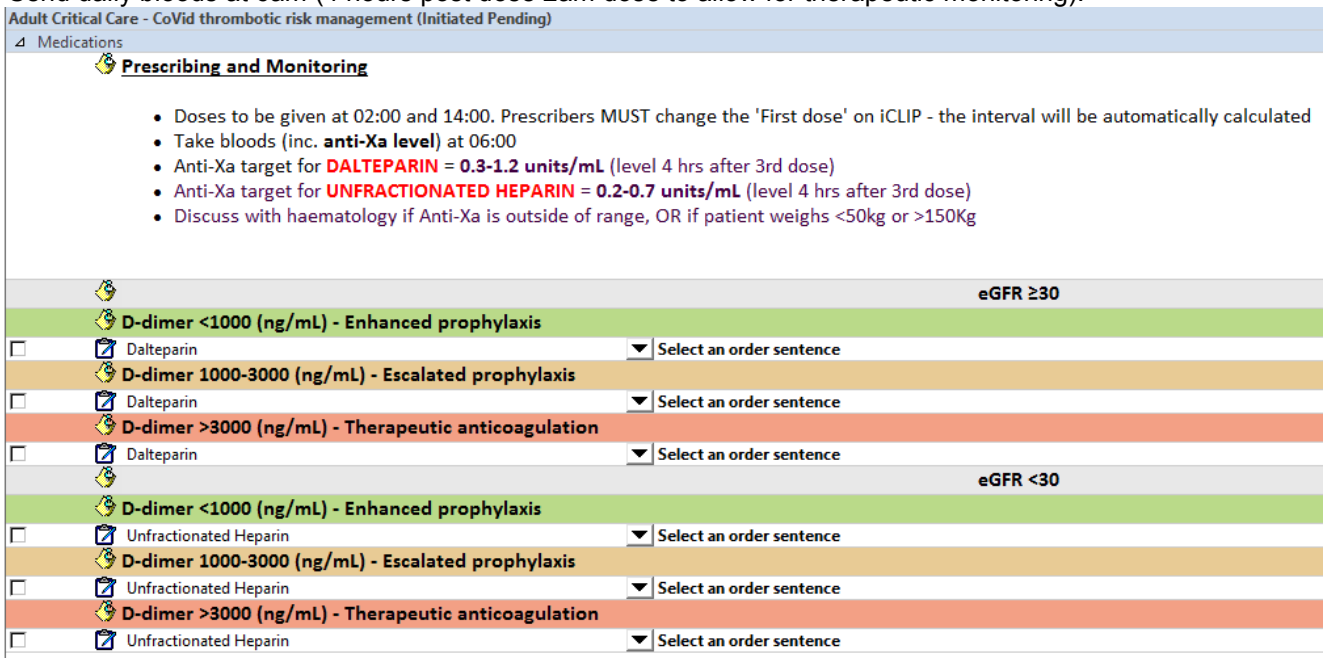
Initial Dosing Table

			Anticoagulant dose *ALWAYS* give by subcutaneous injection		
Renal function	**Anticoagulant choice**	**Estimated ACTUAL body weight (kg)**	**D-dimer <1000ng/ml**	**D-dimer 1000-3000ng/ml**	**D-dimer >3000ng/ml**
eGFR ≥30 ml/min/1.73m^2	**Dalteparin**	<100kg	5000 units 12 hourly	7500 units 12 hourly	10,000 units 12 hourly
		≥100kg	7500 units 12 hourly	10,000 units 12 hourly	15,000 units 12 hourly
eGFR <30 ml/min/1.73m^2	**Unfractionated Heparin (UFH)**	<100kg	10,000 units 12 hourly	15,000 units 12 hourly	20,000 units 12 hourly
		≥100kg	15,000 units 12 hourly	20,000 units 12 hourly	30,000 units 12 hourly

IF <50 OR >150kg discuss dosing with Haematology team

ePrescribing

- Use the "**Adult Critical Care - CoViD thrombotic risk management** "*PowerPlan*" Adult Critical Care - CoVid thrombotic risk management
- **Give at 2am and 2pm**. Prescribers ***MUST*** change the time of the first dose to 02:00 or 14:00, allowing at least 12 h from the previous dose Subsequent doses will automatically be calculated from this based on a 12-hly interval.
- Send daily bloods at 6am (4 hours post dose 2am dose to allow for therapeutic monitoring).



Monitoring

- All patients should have daily measurements of [Hb] / platelet count / INR / aPTTr / fibrinogen / D-dimer **AND** anti Xa
- To be meaningful, anti Xa levels should be measured 4 hours after the THIRD dose of any s/c BD regime or dose change.
- ***DO NOT*** request ***OR*** act upon anti Xa levels during therapy sessions of "continuous" renal replacement therapy.
- ***DO*** request and act on anti Xa levels during periods of intermittent haemodialysis.
- **Anti Xa targets**
  - For Dalteparin 0.3-1.2units/ml
  - For UFH 0.2-0.7units/ml

D-dimer (ng/ml)	<1000	1000-3000	>3000
Dalteparin anti Xa targets	<1.2units/ml	<1.2units/ml	0.3-1.2units/ml
UFH anti Xa targets	<0.7units/ml	<0.7units/ml	0.2-0.7units/ml

  - In essence, anti Xa level monitoring in patients in the **GREEN** and **AMBER** bands of D-dimer levels is for safety i.e. to alert if patients are excessively anticoagulated. If they are, discuss dose titration with the on call Haematology SpR on bleep 6068.
  - In the **RED** band, it is to ensure the dose is achieving heparin activity consistent with therapeutic anticoagulation. Again, if the level is outside of the target range, discuss dose titration with the on call Haematology SpR on bleep 6068.

Dose titration

- During the patient's ICU stay D-dimer levels may vary by apparently large margins day-to-day.
- ***DO NOT*** change the dose of BD s/c Dalteparin / UFH ***UNLESS EITHER:***
  - the ***OVERALL*** trajectory of the patient's COVID-19 disease is ***DETERIORATING*** ***AND*** the anti Xa level is consistently ***LESS THAN*** the lower target limit (regardless of D-Dimer level). In this scenario ***ESCALATE*** therapy under the direction of on call Haematology SpR on bleep 6068.
  - the ***OVERALL*** trajectory of the patient's COVID-19 disease is ***IMPROVING*** ***AND*** the daily D-dimer levels fall "significantly" below the boundary level between the 3 risk categories for 7 (or more) consecutive days. In this scenario ***CONSIDER DE-ESCALATION*** to the lower risk category.
- ***DO NOT OMIT*** any doses ***UNLESS*** the patient has an acute / active bleed - defined as (see also suggest intervention plan IF acute bleeding occurs whilst on anticoagulants):
  - otherwise unexplained drop in [Hb] ≥20g/L in ≤24 hours ***AND / OR***
  - otherwise unexplained haemodynamic instability ***AND / OR***
  - obvious macroscopic haemorrhage e.g. ***FRANK BLOOD*** via nose, mouth, nasogastric tube or per rectum [**NOTE** "coffee grounds" gastric aspirates are not ***IN ISOALTION*** a reliable sign of significant upper GI bleeding; similarly, frank haematuria may represent a small amount of blood in a large volume of urine.]
  - ***IF IN DOUBT, PLEASE SEEK A SENIOR / EXPERT ADVICE***
  - ***PLEASE*** compete a Datix if you suspect a patient suffers a significant bleed and include this event in the weekly M&M.

COVID-19 patients with proven (or strongly suspected) DVT / PE

- ***IF*** anticoagulant drug naïve (i.e. admission diagnosis) ***START THERAPY*** as if D-dimer >3000ng/ml
- ***IF*** occurs whilst on this enhanced prophylaxis regime ***CONSIDER*** starting on **Argatroban** (please discuss with Haematology)
- The clinical threshold to give thrombolysis in the context of a suspected / proven PE should arguably be ***LOWER*** than standard practice
    - ***HOWEVER*** as RV dysfunction is both common and multifactorial in COVID-19 patients, a CTPA to prove the diagnosis AND determine the clot burden should always be performed ***IF POSSIBLE***.
    - ***IF POSSIBLE*** please also seek the advice of Prof Madden's expert team before giving empirical thrombolysis.
- ***DURATION*** of therapy should be a minimum of 3 months ***BUT*** both the duration ***AND*** the optimal agent (e.g. rivaroxaban or warfarin) should be discussed with Haematology

PRIOR TO WARD STEP DOWN FROM ICU [i.e. this is the responsibility of the ICU team]

- ***IF*** the patient has a proven (or strongly suspected) thromboembolic event ***OR*** any other reason for therapeutic anticoagulation (e.g. paroxysmal AF) ***CONTINUE*** the regime the patient is current on
- ***IF*** the patient is on ***ANY*** of the ICU "enhanced prophylaxis" regimes ***CHANGE*** the prescription of Dalteparin / UFH as follows:

Ward Enhanced Prophylaxis Dosing Table

Anticoagulant dose *ALWAYS* give by subcutaneous injection

Renal function	Anticoagulant choice	Estimated ACTUAL body weight (kg)	REGARDLESS OF D-dimer level
eGFR ≥30 ml/min/1.73m^2	**Dalteparin**	<100kg	5000 units at 6am and 6pm
		≥100kg	7500 units at 6am and 6pm
eGFR <30 ml/min/1.73m^2	**Unfractionated Heparin (UFH)**	<100kg	10,000 units at 6am and 6pm
		≥100kg	15,000 units at 6am and 6pm

IF <50 OR >150kg discuss dosing with Haematology team

ENSURE that there is AT LEAST a 12 hour gap between the final ICU dose and the first WARD dose

Extending prophylaxis post hospital discharge

- There is an increasing body of evidence that patients discharged home following an acute emergency admission are at significantly increased risk of VTE due to relative / comparative immobility and often have a pro-thrombotic / hyper-coaguable state.
- There is an absence of evidence to guide best practice in general medical emergency admissions and none in patients admitted with COVID-19 pneumonitis.
- On the basis of an empirical risk verses benefit equation there is a logical augment to discharge patients with on-going pharmacological thromboprophylaxis.
- Given the heterogeneity of the post-ICU patient population, a case by case assessment is required to determine the optimal strategy.

Renal replacement therapy (RRT)

[***THIS IS THE COVID-19 / HYPER-COAGULOPATHY SPECIFIC GUILELINE NOT THE STANDARD GUIDELINE***]

- All patients requiring RRT will be on UFH and ***MUST RECEIVE*** their subcutaneous doses as per schedule ***WHETHER OR NOT*** they are on RRT ***UNLESS*** they have been switched to continuous infusions of **Argatroban**
- ***IF*** the most recent aPTTr <2.0 ***GIVE*** an IV bolus of UFH just before connecting the patient to the filter. The dose of the bolus depends upon the recent D-dimer level (taking the trend into account, if available) and is shown in the table below.
    - ***IF*** the most recent aPTTr ≥2.0 DO NOT GIVE the IV bolus
- Boluses must be prescribed as PRN "heparin flushes".
    - **ePrescribing** - Use the order sentence for "***Unfractionated Heparin IV Flush***" - set this to ***PRN*** and the ***Frequency*** to every four hours.
- In addition, commence a continuous infusion of UFH ***via the filter*** as follows:

D-dimer (ng/ml)	<1000	1000-3000	>3000
Bolus dose of IV UFH on starting RRT	2500units	2500units	5000units
Starting dose of UFH infusion	1000units/hour	1500units/hour	2000units/hour

- Perform an aPTTr every 4 hours aiming for a target of 2.0-4.5. ***PLEASE NOTE*** that COVID-19 / hyper-coaguable patients are likely to have elevated fVIII levels which adversely affect the aPTTr assay and MAY result in falsely low ratios / shortened times.
- Dose titration of the continuous UFH infusion into the filter:
    - The (soft) minimum dose is 500units/hour. The (soft) maximum dose is 4000units/hour.
    - If <2.0, increase dose by 1000units/hour
    - If >4.5, decrease dose by 500units/hour
    - IF aPTTr is consistently >4.5 [***DEFINED AS***: despite infusion reduced to 500units/hour for ≥4hours] ***REDUCE*** the UFH filter infusion from 500 to 200units/hour - ***DO NOT STOP THE UFH UNLESS THE PATIENT IS ACTIVELY BLEEDING***
- Once a stable / effective dose is established ***RECORD THIS CLEARLY*** and use it as the ***STARTING*** dose for the next RRT session
- ***IF*** despite optimal use of this regime ***AND*** VasCath flow / position ***EXCLUDED*** as a problem ***STOP*** all UFH ***AND COMMENCE*** systemic (into the patient) **Argatroban** as per protocol below. ***USE CONTINUOUS*** IV Argatroban ***UNTIL*** off RRT for >48 hours with decision ***NOT*** to restart in the next 24-48 hours.

Argatroban protocol

- Usual presentation is a **MULTI-DOSE** vial of Argatroban containing 250mg in 2.5ml. [Exembol Multidose 100 mg/ml concentrate for solution for infusion]
- For infusion rates ***less than 9.0ml/hr:*** Withdraw 0.5ml (50mg) and dilute in 50ml of cystalloid in a 50ml syringe to make a solution with a concentration of 1mg/ml. ***YELLOW***
- Place the opened vial in the drug fridge having written on the box the date first opened. Storage for 28 days is allowed.
- For infusion rates ***greater than 9.0ml/hr:*** Dilute 250mg (2.5mL) with 250mL NS or D5W (1mg/mL). ***BLUE***

Argatroban 250mg in 2.5ml multi use vial	***Syringe***	**Default:** 0.5mcg/kg/min **Maximum:** 10mcg/kg/min	Dilute 50mg (0.5mL) with 50mL NS, D5W or Hartmanns (1mg/mL)	Use only the multidose vial. Once opened, store in the fridge up to 28 days.
Argatroban 250mg in 2.5ml multi use vial	***Volumatic pump required***	**Default:** 0.5mcg/kg/min **Maximum:** 10mcg/kg/min	Dilute 250mg (2.5mL) with 250mL NS or D5W (1mg/mL)	Use Uncommon Volumat Pump Make a bag only if more than 10mL/hour is required See protocol for dosing guidelines If no uncommon pump, MUST calculate rate in mL/hr Give via Drug X

- Initial Infusion Rate 2mcg/kg/min. Dose titration table shown below and should be guided by aPTTr

aPTTr	Infusion Rate change	Next aPTTr
< 1.5	***INCREASE*** by 0.5mcg/kg/min	2 hours
1.5-3.0	***NO CHANGE***	2 hours After 2 consecutive aPTTr within target range, check with daily bloods
> 3.0 **ON RRT**	***HALF*** of the previous infusion rate	2 hours
> 3.0 **NOT ON RRT**	***STOP*** infusion until the aPTTr is 1.5-3.0; ***RESUME*** at half of the previous infusion rate	2 hours

- Conversion table showing ml/hr infusion rate for dose range and patient weight

DOSE (mcg/kg/min)	**0.5**	**1.0**	**1.5**	**2.0**	**2.5**	**3.0**	**3.5**	**4.0**
Actual body weight (kg)	***Infusion Rate (ml/hr) using dilution of 1mg/ml***							
50	1.5	3.0	4.5	6.0	7.5	9.0	10.5	12.0
60	1.8	3.6	5.4	7.2	9.0	10.8	12.6	14.4
70	2.1	4.2	6.3	8.4	10.5	12.6	14.7	16.8
80	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2
90	2.7	5.4	8.1	10.8	13.5	16.2	18.9	21.6
100	3.0	6.0	9.0	12.0	15.0	18.0	21.0	24.0
110	3.3	6.6	9.9	13.2	16.5	19.8	23.1	26.4
120	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8
130	3.9	7.8	11.7	15.6	19.5	23.4	27.3	31.2
140	4.2	8.4	12.6	16.8	21.0	25.2	29.4	33.6
150	4.5	9.0	13.5	18.0	22.5	27.0	31.5	36.0

- ***USE CONTINUOUS*** IV Argatroban ***UNTIL*** off RRT for >48 hours with decision ***NOT*** to restart in the next 24-48 hours.
- ***ONCE OFF RRT RE-COMMENCE*** UFH subcutaneous regime.
- **Pharmacodynamics:** Argatroban, a synthetic L-arginine derivative, is a direct thrombin inhibitor that binds reversibly to thrombin. Argatroban exerts its anticoagulant effect independently of antithrombin III and inhibits fibrin formation; activation of coagulation factors V, VIII and XIII; activation of protein C; and platelet aggregation.
- **Pharmacokinetics:**
    - Steady-state levels typically achieved within 1-3 hours following initiation.
    - Anticoagulation parameters return to baseline generally within 2 to 4 hours after discontinuation of infusion. There is no reversal agent.
    - Predominantly inactivated by hepatic metabolism. Use with caution / dose reduce in severe hepatic impairment.
    - No significant clearance on RRT
- **NOTE:**
    - Argatroban will result in an elevated INR but this should not be used to titrate therapy.
    - Argatroban interferes with the Fibrinogen lab assay resulting in falsely low levels. If assessment of Fibrinogen required during therapy perform a TEG as the functional fibrinogen (CFF) assay should not be affected.

This guideline has been peer reviewed by: James Uprichard, Steve Austin, Pamala Kanagasabapathy, Paul Grayston and Joanne Peh.

References

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2. April 6, 2020. Disseminated pulmonary microvascular thromboembolism in COVID-19: a mechanistic link between coagulopathy and respiratory failure? anne sofie andreasen, MD, PhD, EDIC | Department of Anesthesiology and Intensive Care, Herlev and Gentofte Hospital, Denmark Comments on https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184
3. Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7167301/
4. Dosing loosely based upon https://www.dbth.nhs.uk/wp-content/uploads/2017/10/Dalteparin_Dosing_Tables.pdf [in particular, taking treatment doses in pregnancy as the guide in patients with D-dimer >3000].
5. Evidence of benefit from therapeutic anticoagulation in COVID-19 infection https://www.ncbi.nlm.nih.gov/pubmed/32387623 and https://www.ncbi.nlm.nih.gov/pubmed/32220112

Critical care quick reference guide

Thrombotic risk management in COVID-19

Suspected / confirmed COVID-19 infection with features of hyper-inflammatory syndrome

Exclusion criteria

- Platelets <50 x 10^9/L
- Fibrinogen <2.0 g/L
- APTR / INR >2 (if anticoagulant naïve)
- Suspected / overt active bleeding

→ **Discuss urgently with haematology if any apply**

Pharmacological thromboprophylaxis	**Anticoagulation for proven / likely thromboembolism**	**Clot prevention in renal replacement therapy**
Dose stratification by most recent D-dimer concentration	Use 'therapeutic anticoagulation' dosage column below **and** discuss with haematology	**Refer to guidance in full thromboprophylaxis protocol**

eGFR
mL/min/1.73 m^2

eGFR ≥30: Dalteparin
Subcutaneous, 12-hly at **02:00** and **14:00**

Body weight	**D-dimer** (ng/mL) <1000	**D-dimer** (ng/mL) 1000–3000	**D-dimer** (ng/mL) >3000
50–99 kg	Dalteparin 5000 units SC 12-hly	Dalteparin 7500 units SC 12-hly	Dalteparin 10000 units SC 12-hly
100–150 kg	Dalteparin 7500 units SC 12-hly	Dalteparin 10000 units SC 12-hly	Dalteparin 15000 units SC 12-hly
Seek haematology advice if <50 or >150 kg	Enhanced prophylaxis	Escalated prophylaxis	Therapeutic anticoagulation

Anti-Xa target range: **0.3–1.2** units/mL

eGFR <30: Unfractionated heparin
Subcutaneous, 12-hly at **02:00** and **14:00**

D-dimer (ng/mL) <1000	**D-dimer** (ng/mL) 1000–3000	**D-dimer** (ng/mL) >3000
Heparin 10000 units SC 12-hly	Heparin 15000 units SC 12-hly	Heparin 20000 units SC 12-hly
Heparin 15000 units SC 12-hly	Heparin 20000 units SC 12-hly	Heparin 30000 units SC 12-hly
Enhanced prophylaxis	Escalated prophylaxis	Therapeutic anticoagulation

Anti-Xa target range: **0.2–0.7** units/mL

Prescribing and monitoring

- Prescribe using the **Adult Critical Care - CoViD thrombotic risk management PowerPlan**
- Set the first dose to **02:00** or **14:00**, allowing **at least 12 h** from any previous dose
- Take bloods (inc. **anti-Xa level**) at 06:00, 4 h after the 02:00 dose
- Anti-Xa level is interpretable after 3 stable doses; discuss with haematology if outside target range

Quick reference guide v1.0
Based on protocol v7.0
AH April 2020