CRASH-19

Aspirin, losartan & simvastatin in hospitalised COVID-19 patients: a multinational randomised open-label factorial trial

Managing your drug supply - site guidance

CRASH-19 Aim

- To assess the effectiveness and safety of supportive care interventions for patients hospitalised with suspected or confirmed acute COVID-19 infection with a focus on heart and lung protection

- To evaluate the effects of **aspirin, losartan, and simvastatin** in patients with suspected or confirmed acute COVID-19 infection compared with standard care

Managing Trial Drug at Site

- Sites will receive trial drugs from their National Coordinating Centre (NCC)
- Principal Investigators must identify a suitably trained person (ideally a pharmacist) to be responsible for overseeing the receipt, dispensing and accounting for the trial drugs
- The trial will use any brand of aspirin, losartan and simvastatin approved in your country
- Trial drugs should be kept in a secure drug storage cupboard on the COVID-19 ward or in the hospital pharmacy
- The trial drugs should be stored and managed in accordance with the drug instruction label and local policy for storage and handling of prescription medicines
- **Use of the trial drugs for non-trial patients is prohibited and is a serious breach of the trial procedure**

Trial Treatments

- Eligible and consenting patients will be randomised to one of the following treatment arms via the trial database:

- Arm 1: Aspirin 150 mg
- Arm 2: Losartan 100 mg
- Arm 3: Simvastatin 80 mg
- Arm 4: Aspirin 150 mg and Losartan 100 mg
- Arm 5: Aspirin 150 mg and Simvastatin 80 mg
- Arm 6: Losartan 100 mg and Simvastatin 80 mg
- Arm 7: Aspirin 150 mg, Losartan 100 mg and Simvastatin 80 mg
- Arm 8: Standard care control (no additional treatment)

Treatment is given once daily until discharge, death, or 28 days after randomisation. For drug and dose rationale, please review the Trial Overview Presentation

Receiving Trial Drug Stock

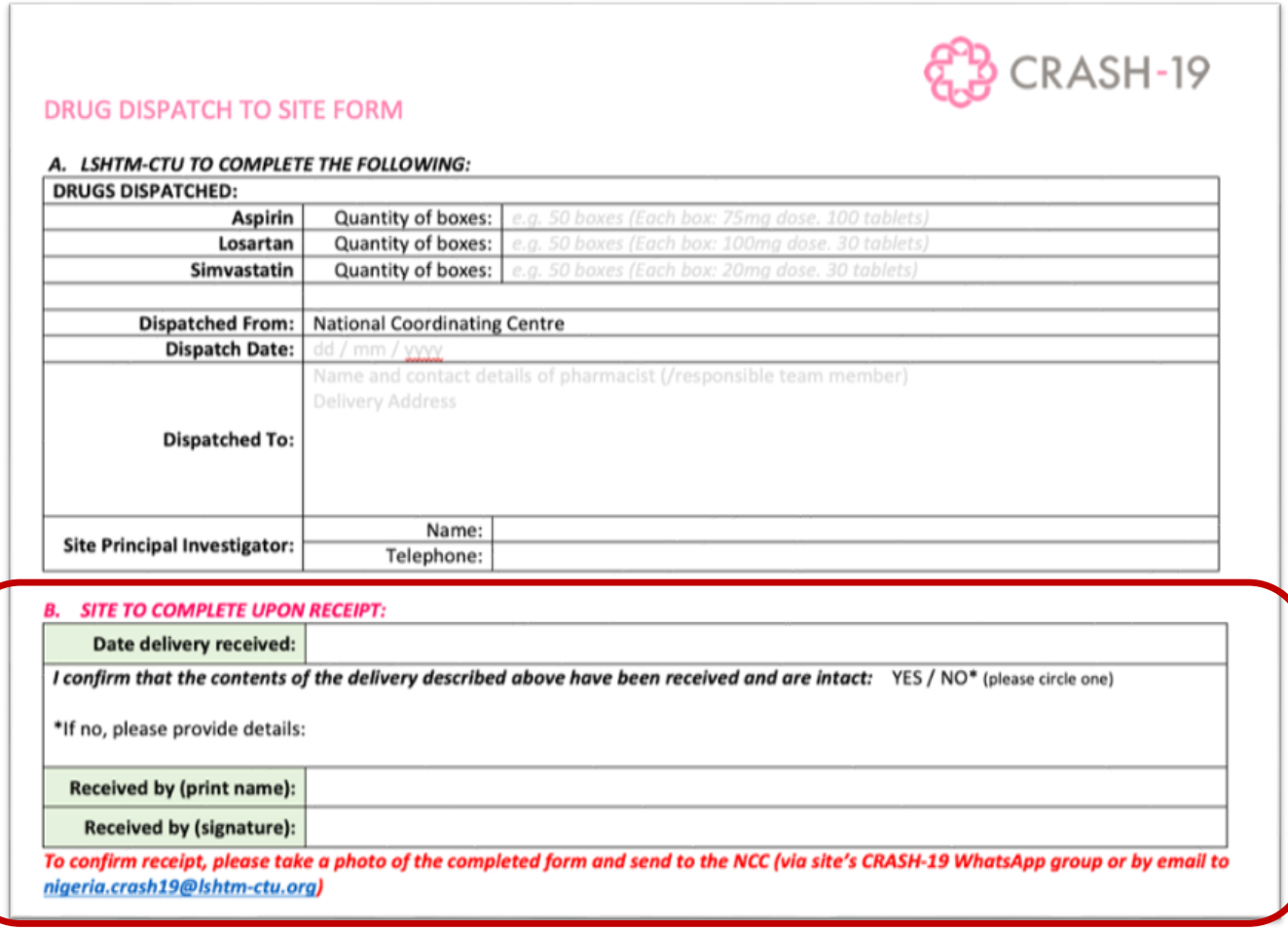
- Sites will receive an initial batch of trial drugs for 50 patients

- The shipment will be addressed to the PI and named trial pharmacist / team member responsible for drug management

- Each drug shipment sites receive will contain:
  - Batch of trial drugs
  - Drug Dispatch to Site Form - to confirm receipt of the trial drugs
  - Site Pharmacy Dispensing Logs – to document dispensing details and unused/destroyed trial drugs

Confirming Receipt of Trial Drugs

- Upon receipt of a delivery of trial drugs from the NCC, complete SECTION B of the accompanying **Drug Dispatch to Site Form**
- Send a photo of the completed form to the NCC via your site CRASH-19 WhatsApp group / by email



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DRUG DISPATCH TO SITE FORM

A. LSHTM-CTU TO COMPLETE THE FOLLOWING:

DRUGS DISPATCHED:		
Aspirin	Quantity of boxes:	e.g. 50 boxes (Each box: 75mg dose. 100 tablets)
Losartan	Quantity of boxes:	e.g. 50 boxes (Each box: 100mg dose. 30 tablets)
Simvastatin	Quantity of boxes:	e.g. 50 boxes (Each box: 20mg dose. 30 tablets)
Dispatched From:	National Coordinating Centre	
Dispatch Date:	dd / mm / yyyy	
Dispatched To:	Name and contact details of pharmacist (/responsible team member) Delivery Address	
Site Principal Investigator:	Name:	
	Telephone:	

B. SITE TO COMPLETE UPON RECEIPT:

Date delivery received:	
I confirm that the contents of the delivery described above have been received and are intact: YES / NO* (please circle one) *If no, please provide details:	
Received by (print name):	
Received by (signature):	

To confirm receipt, please take a photo of the completed form and send to the NCC (via site's CRASH-19 WhatsApp group or by email to nigeria.crash19@lshtm-ctu.org)

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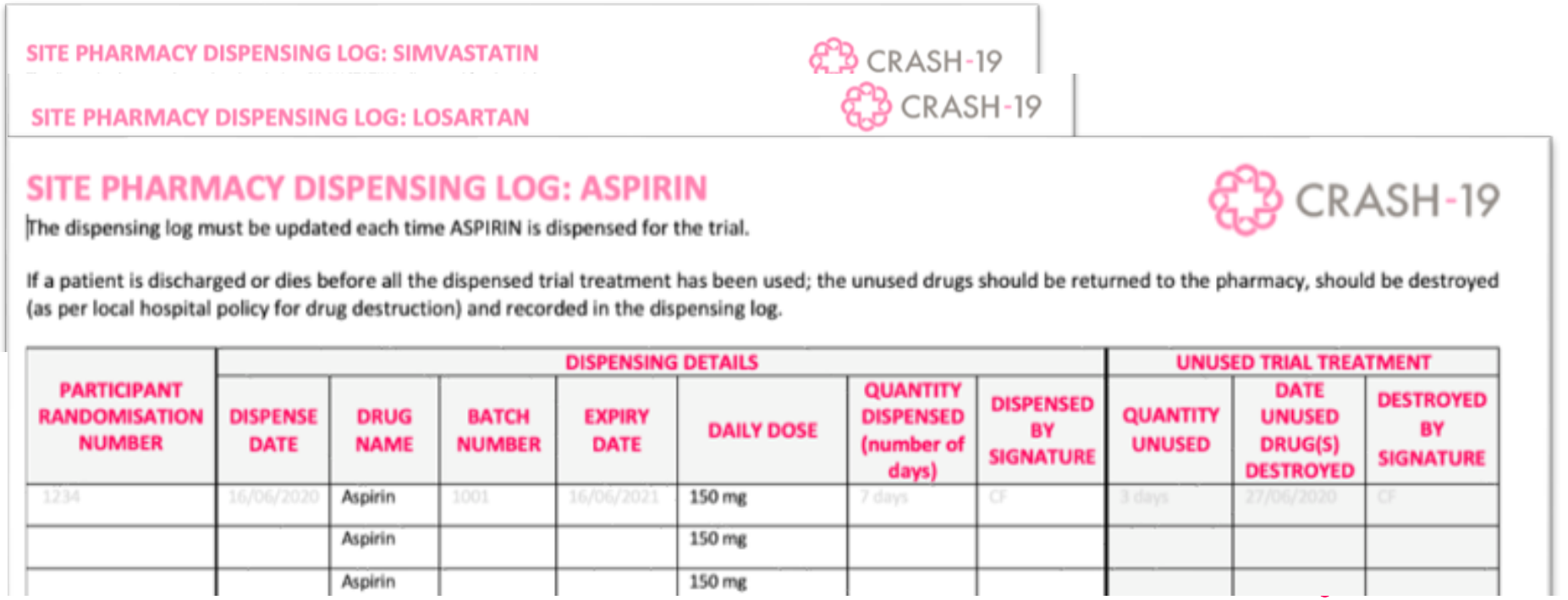
Dispensing Trial Drugs

- Patients are randomised via the trial database
- After randomisation, an email will be sent to the person carrying out the randomisation confirming which trial drug(s), if any, should be given to a patient
- Trial drug(s) must only be provided to trial participants and are free of charge
- Trial drug(s) must be prescribed (by a clinician) on the drug prescription chart (or where all other routine drugs are prescribed)
- Trial drug(s) should be dispensed by a pharmacist or other named responsible person
- To avoid waste, the person responsible for dispensing is advised to dispense the trial treatment in 7 day instalments, up to a maximum of 28 day supply:
- Example dispensing quantities for 7 days:
  - **28 tablets of Simvastatin** (20mg tablets: 10 tablets per blister packs; 3 blister packs per box)
  - **14 tablets of losartan** (50mg tablets: 10 tablets per blister packs; 3 blister packs per box)
  - **14 tablets of Aspirin** (75mg tablets: 10 tablets per blister pack; 10 blister packs per box)

Dispensing Trial Drugs

- Corresponding **Site Pharmacy Dispensing Log** to be updated when:
  - drugs are dispensed for the trial
  - unused trial drugs are returned for destruction
- The pharmacist / delegated team member, will be responsible for updating the Site Pharmacy Dispensing Logs
- Copies of the Site Pharmacy Dispensing Logs should be sent to the NCC weekly via your site CRASH-19 WhatsApp group / email



SITE PHARMACY DISPENSING LOG: SIMVASTATIN

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SITE PHARMACY DISPENSING LOG: LOSARTAN

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SITE PHARMACY DISPENSING LOG: ASPIRIN

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The dispensing log must be updated each time ASPIRIN is dispensed for the trial.

If a patient is discharged or dies before all the dispensed trial treatment has been used; the unused drugs should be returned to the pharmacy, should be destroyed (as per local hospital policy for drug destruction) and recorded in the dispensing log.

PARTICIPANT RANDOMISATION NUMBER	DISPENSING DETAILS							UNUSED TRIAL TREATMENT		
	DISPENSE DATE	DRUG NAME	BATCH NUMBER	EXPIRY DATE	DAILY DOSE	QUANTITY DISPENSED (number of days)	DISPENSED BY SIGNATURE	QUANTITY UNUSED	DATE UNUSED DRUG(S) DESTROYED	DESTROYED BY SIGNATURE
1234	16/06/2020	Aspirin	1001	16/06/2021	150 mg	7 days	CF	3 days	27/06/2020	CF
		Aspirin			150 mg					
		Aspirin			150 mg					

Administering Trial Drugs

- Trial drug(s) to be given once daily (until discharge, death or 28 days after randomisation, whichever is shorter) or if the responsible clinician decides to cease treatment for clinical reasons
- Please ensure a trial team member is identified every day to make sure patients receive their allocated drugs
- To avoid confusion, prescribed drugs to be taken in the morning so that trial drug administration happens at the same time every day
- Multiple tablets may need to be taken to achieve required dose e.g. 4 x 20mg Simvastatin
- All trial drug(s) given to a patient must be signed off as given on the drug chart/or equivalent

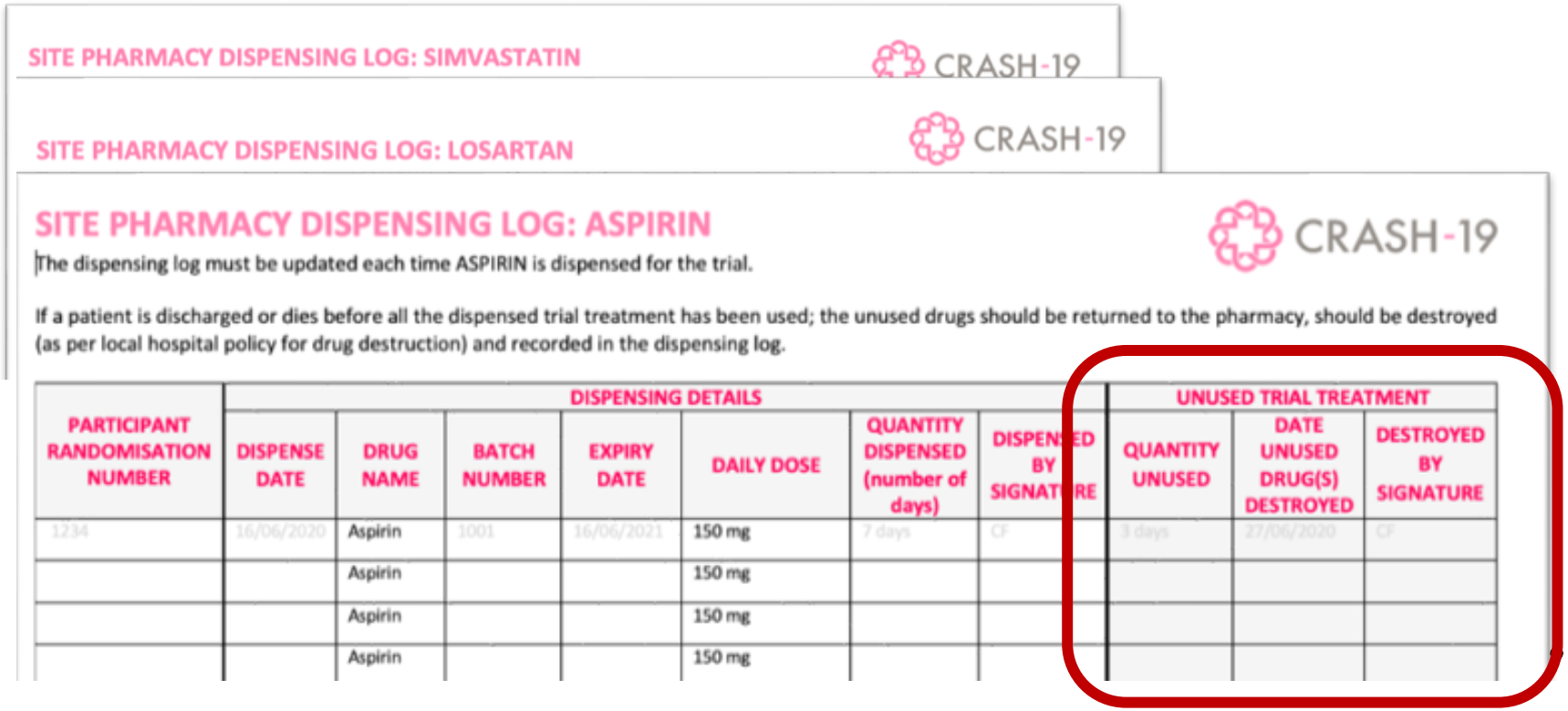
Administering Trial Drugs

- If a patient is unable to take oral tablets e.g. if the patient requires mechanical ventilation after randomisation, drugs can be administered via alternative enteral routes if available (e.g. nasogastric tube or other naso-enteric feeding tubes)

- ***Losartan dose variation***:
  - If any contraindication develop after randomisation (e.g. hypotension or hyperkalaemia or hypotension) the dose can be reduced to 50mg or stopped. Treatment can be restarted at any time up to the end of the treatment period when these problems are resolved.

Unused Trial Drugs

- If a patient is discharged or dies before the full amount of dispensed trial treatment has be used, the unused trial treatment should be returned to the trial pharmacist / responsible team member
- Returned drugs should be **destroyed** as per the hospitals local policy for drug destruction
- The quantity of returned unused drugs and the date of drug destruction should be recorded in the corresponding **Site Pharmacy Dispensing Log**



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		Aspirin			150 mg					
		Aspirin			150 mg					
		Aspirin			150 mg					

Monitoring Trial Drug Stock

- A minimum stock level will be agreed for each site after the first 2 weeks of recruitment

- Trial drug stock at site will be monitored by NCC and LSHTM-CTU:
  - through the number of entry forms submitted to the trial database
  - review of the Site Pharmacy Dispensing Logs

Information about the Trial Drugs

- The trial treatments are commonly used drugs, please consult the packet inserts for information
- More detailed information can be found in the 'Summary of product characteristics' available in the electronic Investigator Site File (eISF 1), folder 2, on the trial website (crash19.lshtm.ac.uk) and can be downloaded by clicking the links below:

  - Aspirin - click here to download
  - Losartan - click here to download
  - Simvastatin – click here to download

- Appendix 1 of the trial protocol summarises key contraindications to the trial treatments.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

CLINICAL TRIALS UNIT

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