

PRINCIPLE Trial SUSAR Update

PRINCIPLE Study <principle@phc.ox.ac.uk>

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To: Rebecca Lowe <rebecca.lowe@phc.ox.ac.uk>

PLEASE NOTE THAT THIS EMAIL IS BEING SENT TO ALL PRINCIPAL INVESTIGATORS AT OPEN PRINCIPLE SITES.

Dear Colleague,

We would like to update you on the **PRINCIPLE trial** and provide some important details regarding a SUSAR. As part of our safety reporting requirements, we are informing you of a "Suspected Unexpected Serious Adverse Reaction" (SUSAR). This is the second SUSAR reported in the trial.

As you are aware, any Serious Adverse Event (SAE) thought to be related to Ivermectin, by either the Principal Investigator (PI) or the Chief Investigator/Safety Delegate, is classified in the protocol as a SUSAR in accordance with the Investigator's Brochure.

We are sharing the details with all site PIs in the interests of transparency.

Details of the SUSAR are listed below, which was reported to the Sponsor and MHRA on 02-Sep-2021:

What happened?

This participant was randomised to Ivermectin on 17th August 2021. The participant was taking bisoprolol which was stopped before joining the trial. Tachycardia was noted on 20th August 2021 when attending a health care visit for routine bloods. Participant started feeling unwell on the 26th August 2021 and was admitted to the hospital. On the 28th August 2021, bisoprolol was resumed and participant started feeling better with a heart rate within normal range. The participant had completed the full course of Ivermectin on 21st August 2021. The SAE was reported as resolved on 28th August 2021.

What was the response?

All study procedures were followed as appropriate. The clinician assessing the SAE considered that this was **possibly related** to taking ivermectin and hence categorised it as a SUSAR.

Overall, this is a good example of protocol adherence and we do not intend to change any trial procedures as a result. The participant continued in the trial and was followed up as normal for the 28 day follow up period. **There are no further updates expected regarding this SUSAR.**

Please do remain vigilant for anything that constitutes a SAE throughout your patients' time on the trial and inform the trial team within 24 hours of becoming aware.

Please do get in touch with the trial team on principle@phc.ox.ac.uk if you have any concerns, and please pass this information on to anyone else working on the PRINCIPLE trial at your practice.

Please ensure you file this email in section 13.4 of your PRINCIPLE **electronic Investigator Site File**.

To date, the PRINCIPLE trial has recruited **8728** participants. This is an amazing achievement, and we thank you all for your continuous hard work and support with this important trial.

You will note that we recently updated the timings for new patient registrations to the PRINCIPLE trial to allow continued successful recruitment during this busy period. Registrations are now available from 09:00-10:30 and between 15:30-17:30, Sunday - Thursday. Recruitment is currently open to Ivermectin + Usual Care, Favipiravir + Usual Care, and Usual Care alone.

We will continue to monitor registration/screening rates over the coming days and adjust this new policy as necessary in order to maximise effective recruitment into the trial.

Thank you again for all of your hard work and please do not hesitate to get in touch if you have any queries.

Your sincerely,
The PRINCIPLE Trial Team