Defining phenotypes and treatment effect heterogeneity to inform acute respiratory distress syndrome and sepsis trials: secondary analyses of three RCTs

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Plain English summary

Defining phenotypes and treatment effect heterogeneity

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Plain English summary

In this project we studied two common conditions that often necessitate admission to an intensive care unit: sepsis and acute respiratory distress syndrome. We found that, although numerous medical treatments are used to treat patients with these two conditions, studies have shown that they have limited success in reducing the risk of dying.

We hypothesised that clinical trials have failed to show benefit because of differences between participants, such that the treatments benefit some patients but harm and/or show no benefit or harm in other patients. To test this theory, we obtained ethics approval to examine, in two separate analyses, clinical and laboratory data from two sepsis trials and one acute respiratory distress syndrome trial.

The first analysis explored whether or not trial participants' risk of dying affected how the treatments worked (referred to as heterogeneity of treatment effect analysis). The treatment effect of the drugs tested in the sepsis trials did not vary with differences in risk of dying, whereas the drug tested in the acute respiratory distress syndrome trial (simvastatin) probably benefited patients with the lowest risk of dying.

The second analysis explored whether or not patients with these conditions can be divided into subgroups in which the treatments have different effects (referred to as latent class analysis). In the case of sepsis, we identified two sepsis subgroups in one trial and three sepsis subgroups in the other trial but found no differences in treatment effect between subgroups in either trial. In the acute respiratory distress syndrome trial we identified two subgroups, and found that treatment was more beneficial in one subgroup.

Our analysis highlights the value of finding participants with greater similarities (subgroups) within sepsis and acute respiratory distress syndrome to help design future clinical trials.

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