JRMO Research Protocol for Interventional Studies

Full Title	**Therapy for Hepatitis C virus (HCV) in primary treatment failure in Pakistan**
Short Title	HCV in Pakistan
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1. Statistical considerations

1.1 Sample size

Assuming 65% of participants achieve SVR following 12 weeks of Sofosbuvir/Velpatasvir therapy (control condition) and the minimum clinically important difference is a risk ratio of 1.31 so that 85% of participants achieve SVR following 24 weeks of therapy (intervention condition) then 107 participants providing outcome information in EACH GROUP will allow a true risk ratio of 1.31 to be detected with 90% power at the 5% significance level. We will aim to recruit 134 participants to each group (268 in total) to allow for up to 20% loss to follow-up. An increase to 85% SVR is likely to be needed for routine 24-week therapy to be cost-effective.

1.2 Method of analysis

A detailed statistical analysis plan will be written and made publicly available before having sight of the data. Estimates of the treatment effect on clinical outcomes will follow the intention-to-treat principle, with all participants with data on an outcome measure contributing to the analysis in their allocated treatment group. The treatment effect on the primary outcome measure, sustained virologic response, will be estimated as an odds ratio in a logistic regression model, and presented with its 95% confidence interval and p-value. The model will have one binary covariate distinguishing the two treatment groups, and a second binary covariate distinguishing those participants with cirrhosis (stratification variable for the random allocation). This approach will be adapted to secondary clinical outcome measures. Any subgroup analyses will be pre-specified in the statistical analysis plan, with the results being cautiously interpreted.