JRMO Research Protocol for Interventional Studies

Full Title	**Treating hepatitis C in Pakistan. Strategies to avoid resistance to antiviral drugs**
Short Title	HCV in Pakistan
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1. Statistical considerations

1.1 Sample size

Around 25,000 participants will be recruited based on power calculations by our study statistician. Incidence in the high prevalence settings (10% or over) where we will be screening is likely to be around 1.0 per 100 person-years (/100pyrs) based on our modelling. Our aim is to detect incidence rates with sufficient precision to allow robust modelling and to detect (through questionnaires) major risk factors associated with heightened infection risk, so justifying significant investment to reduce their impact. From discussion with Pakistani colleagues, we chose a risk ratio (RR) >1.8 as sufficient to justify major public health investment.

For the primary incidence study, 20,000 participants with 80% follow-up (16,000) would estimate a true incidence of 1.0/100pyrs with 95% confidence intervals 0.85 to 1.17/100pyrs. Assuming 25% are exposed to a significant risk factor, 16,000 participants give 92% power at 5% significance to detect a true increase in risk from 0.83/100pyrs in unexposed to 1.5/100pyrs in the exposed (RR=1.81). Given that these are uninfected individuals and therefore may be at lower risk, consider a risk factor to which 10% are exposed, 16,000 participants would give 84% power at 5% significance to detect an increase in risk from 0.91 to 1.8/100pyrs in the exposed (RR=1.98).

For the reinfection incidence study, we need 5,000 treated patients to generate sufficient subjects for the treatment failure trial. Given 4,000 'cured' participants in follow-up, we would estimate a true incidence of 1.0/100pyrs with 95% confidence interval 0.72 to 1.36/100pyrs. Given prior infection these individuals are likely to have been exposed to a significant risk factor in the past. So assume a risk factor is present/absent and 25% are exposed, 4,000 participants gives 82% power at 5% significance to detect an increase in risk from 0.70/100pyrs in unexposed to 1.9/100pyrs in the exposed (RR=2.71). Hence, we will be able to detect strong, on-going risk factors for re-infection that justify intervention in those receiving treatment.

In addition, 400 subjects with hepatocellular carcinoma will be recruited. This sample size has been determined empirically based on previous studies in this area that have studied samples of this size.