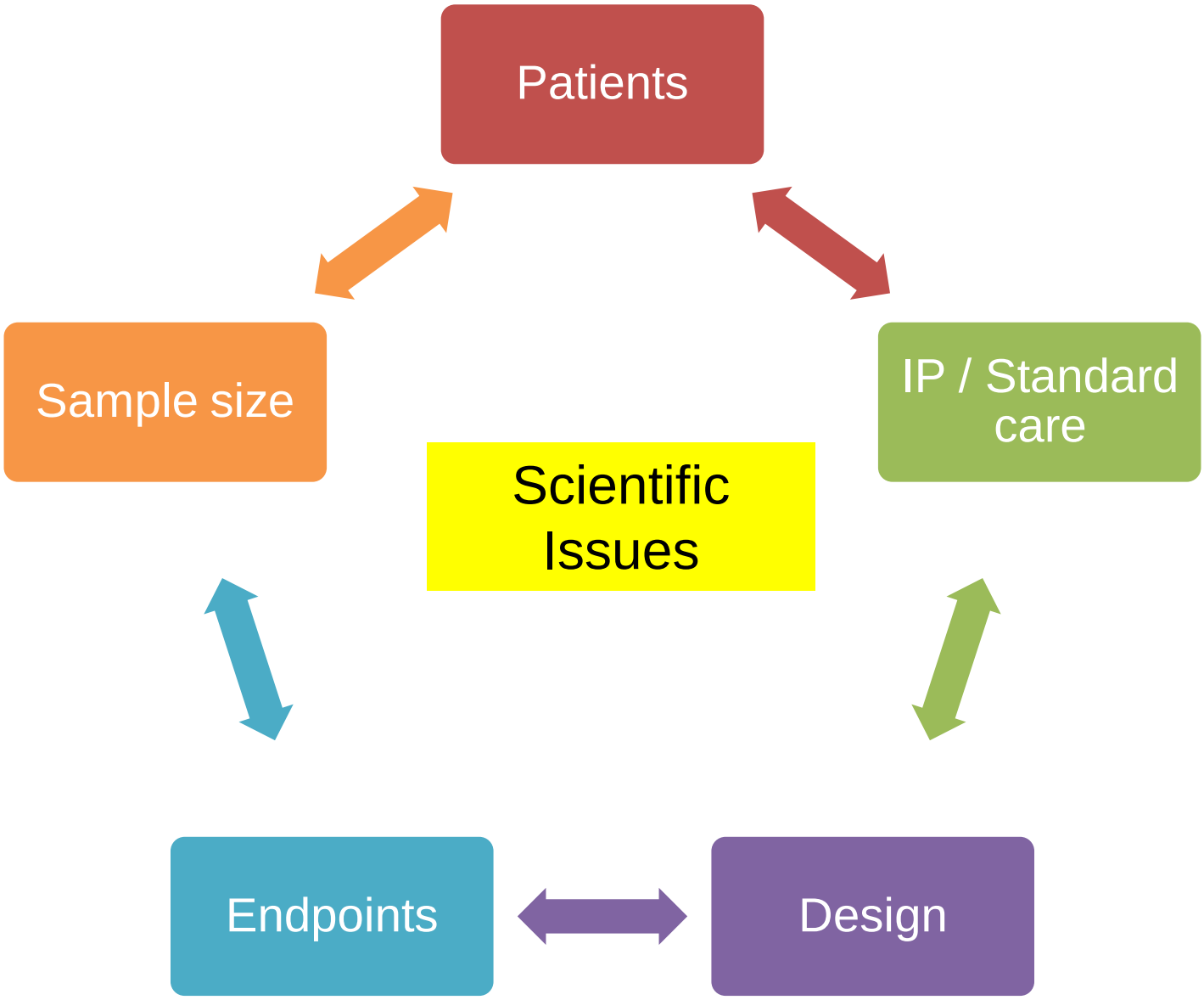
Scientific and Ethical Issues in Covid-19 Clinical Trials

Dr Arun Bhatt MD FICP FICR (UK)
Consultant –
Clinical Research & Development


Patients
Sample size
IP / Standard care
Scientific Issues
Endpoints
Design

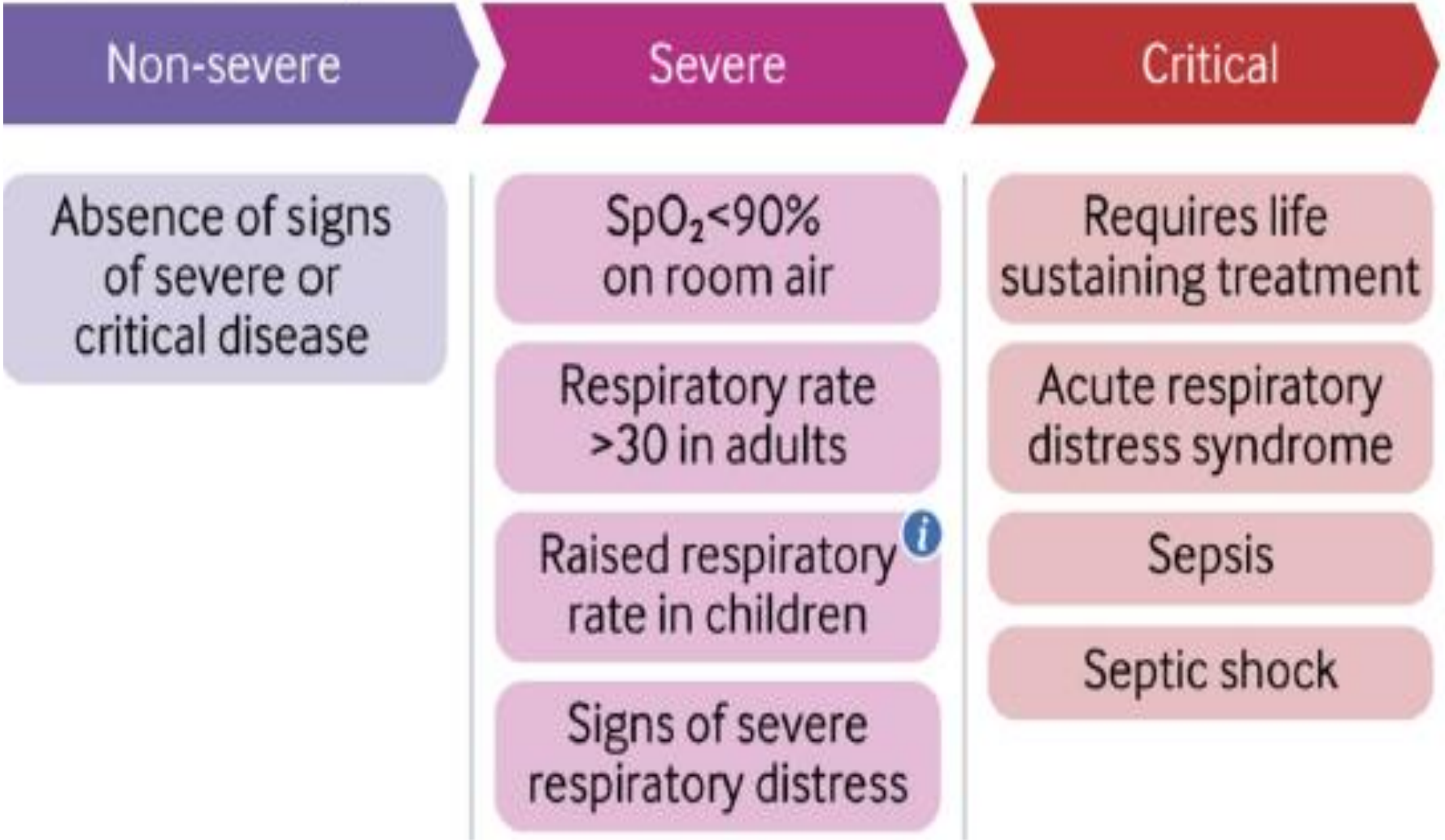
GCP Challenges : Covid-19

- Benefits of investigational / repurposed therapy unknown/unsupported vs. Risks unknown / uncertain
- Interest of science / society overriding interest of individual participant
- Available non-clinical & clinical information on therapy inadequate
- Clinical trials – challenge of science and ethics
- Sponsor and investigator - training and experience in pandemic /trials

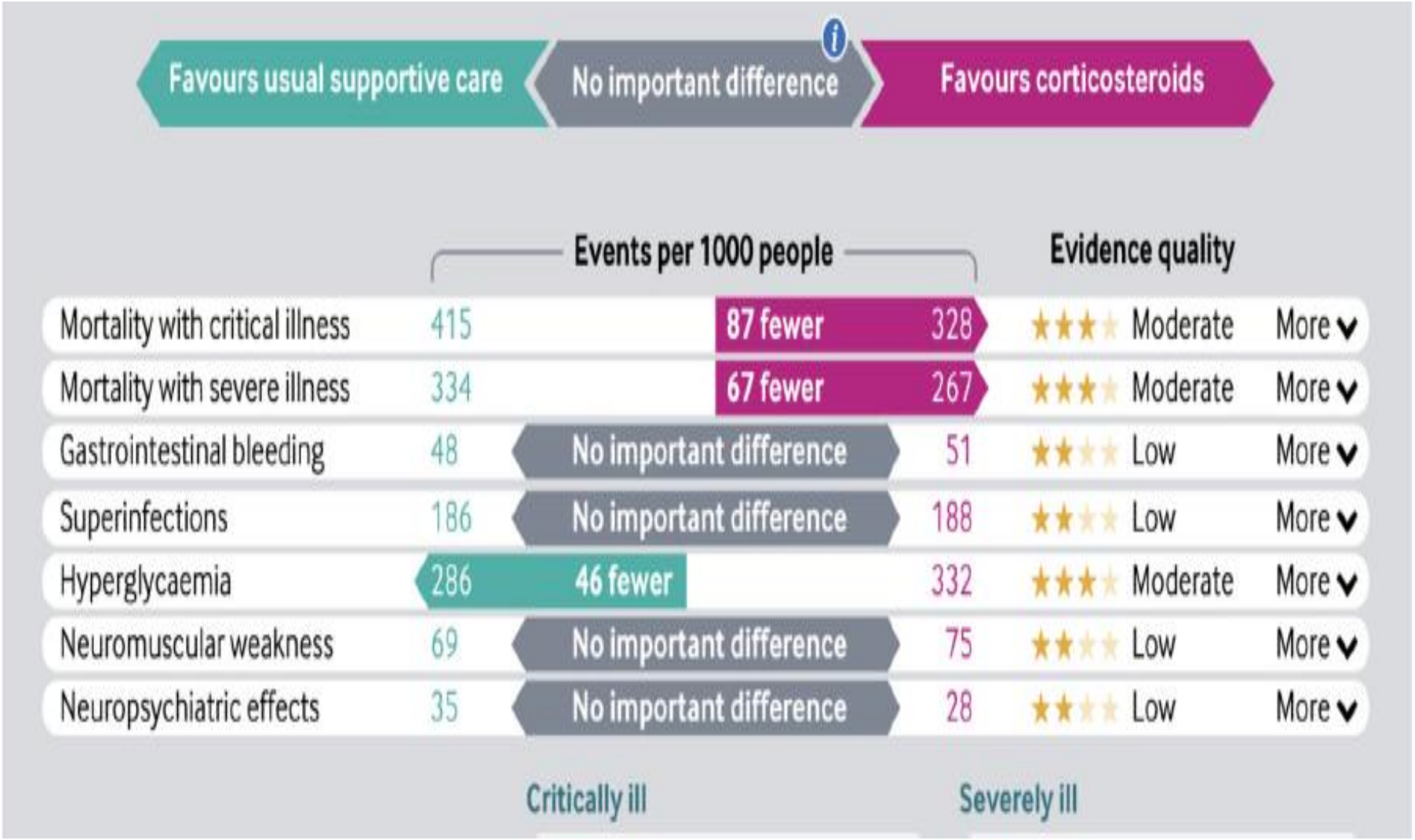
Bias in COVID-19 RCTs (BMJ 31 Jul20)

- Randomisation process
- Departures from the intended intervention
- Missing outcome data
- Measurement of the outcome
- Selection of the reported results
- 21 of 23 RCTs high or high risk of bias in the domains of randomisation or deviation from the intended interventions.

Disease Severity : WHO



Corticosteroids : WHO Recommendation (BMJ 4 Sep20)



Clinical Trials on COVID-19- Examples

Protocol	Remdesivir	Favipiravir	Tocilizumab	Itolizumab
Patients	• **1063** • Severe 89% • Non-severe 11%	• **150** • Mild to moderate	• **243** • Severe	• **30** Moderate to severe
Design RCT	Double blind Placebo	Open Standard care	Double blind Placebo	Open Standard care
Efficacy end points	• Shorter time to recovery • No effect on mortality	• Viral clearance faster • Clinical cure higher %	• Not effective for preventing intubation or death	• Significant Mortality benefit
Published	• Yes	• No	• Yes	• No

Covid-19 Trials : Participants

- **Trial Patients**
  - Vulnerability vs Voluntariness
  - Recruitment
  - Informed Consent process
    - Timing of consent
    - Time for explanation
    - Time for participant
    - Communication
    - Non-availability of LAR
    - Documentation – AV recording

- **Vaccine Volunteers**
  - Vulnerability vs Voluntariness
  - Recruitment
    - Hospital staff
    - Media / social media advertisement
  - Concerns about visiting hospitals
  - Informed Consent process

RECOVERY Trial Informed Consent Process (Oxford)

- For patients **who lacked capacity to consent** due to severe disease requiring ventilation, and for **whom an LAR was not available**, randomization could be done with consent provided by a treating physician, who was independent of the investigator conducting the clinical trial, and who would act as the legally designated representative.

- Consent would be obtained from the patient's LAR or directly from the patient if they recover promptly at the earliest opportunity.

Ethical Responsibilities For Vulnerable Participants (ICMR 2017 & 2020)

Sponsor	• Justification for inclusion • Provisions for protecting safety • Enable monitoring and quality assurance
Investigator	• Recognition of vulnerability • Ensure additional safeguards for protection • Empower the participant to make decisions • Respect dissent from the participant • Avoid exploitation/retaliation/reward/credits • Well-documented informed consent process
Ethics Committee	• Review of justification for inclusion • Careful assessment risk- benefit, and risk minimization • More frequent review and monitoring