MRC MRP-NIHR Trials Methodology Research Partnership PhD Project

(a) *The proposed PhD topic area(s) or title(s):*

Statistical Methods for analysing Longitudinal Ordinal Data in Emergency and Critical Care Clinical Trials

(b) *The host University and Department:*

The University of Warwick, Warwick Clinical Trials Unit

(c) *Lead Supervisors:*

Professor Ranjit Lall and Professor Gavin Perkins

(d) *The academic background required by the student for a particular topic identified:*

MSc in Medical Statistics/Statistics

(e) *Description of the Project:*

In studies of life threatening emergencies, global functionality as captured by outcomes such as the modified Rankin Scale (mRS), Cerebral Performance Category (CPC) score and the Glasgow Outcome Scale Extended (GOS-E) are key indicators of disability and neurological impairment. Each of these outcomes are presented on an ordinal scale: the mRS is a 7-level ordered categorical scale capturing levels of patient functional independence, with scores ranging from 0 (fully independent) to 6 (dead); the CPC score ranges from 0 (good cerebral performance) to 5 (brain death) and GOS-E ranges from 1 (death) to 8 (upper good recovery). These outcomes assist clinicians to understand how neurological recovery transitions over time, for patients who have had a traumatic injury or cardiac arrest. The finer granularity in the scaling of these outcomes aims to provide an insight into the changes of neurological impairment when data are collected over several time points. However, in practice, when these outcomes are analysed, they are very often transformed into binary scales- for example the CPC scores are widely dichotomised into 'good' (CPC 1-2) versus 'poor' (CPC 3-5). The CPC scores have a further added problem in as much that the binary categorisation means that a large proportion of data, which is on the deaths is not taken into account. The main reason for collapsing the categories is that statistical methods, which account for the ordinal nature of the scale are not very well researched and even less so when taking account of change over time. If methods do exist, such as ordinal regression models, they are not necessarily easy to implement and model assumptions can be quite stringent.

The primary aim of this project is to analyse longitudinal ordinal data as collected on neurological outcomes using appropriate statistical methods, in the view to provide results that are clear and meaningful to clinicians.

This project will use data that have been collected on 3 large critical care clinical trials (PARAMEDIC I, PARAMEDIC 2 and SOS). In the PARAMEDIC I trial which randomised 4471 patients, we collected cognitive functioning data on survivors at 3 and 6 months using the CPC scores. Similar data was also collected on 8014 patients for the PARAMEDIC II study and

using the mRS scale at the same time points. For the SOS trial, the GOS-E is the primary outcome measure and we hope to collect this on 638 patients at 6 and 12 months. We will also explore gaining access to other recent UK trials conducted in the emergency and critical setting.

This is a very exciting project which will explores statistical methodology that is at the heart of clinical trials. It will use data from studies published in high impact journals. The studentship programme will involve carrying out a literature review and exploring methods, such as transitional probabilities (over time) and longitudinal regression models. There is also an element of clustering which will need to be accommodated in the P1 trial, which was cluster-randomised. The student will work in a high-quality environment of clinical trials and therefore will be exposed to challenges that are encountered when explaining complex methods to clinicians.

It is envisaged that the output from this PhD will provide new insights for the clinical and statistical community in the best approaches to use for future analyses of clinical trials.

(f) ***Start date of project:*** End of Oct 2019