Progress against HOD1: Methods research to support the use of observational data in healthcare decision making

At the meeting of 17 May 2018, the MRC-NIHR Methodology Research Panel recommended two awards relevant to the HOD1 highlight notice for funding. Further awards under this highlight notice will only be considered where applicants can demonstrate they are targeting a remaining area of need that will not be covered via the below awards:

Grant ref: MR/R025215/1

PI: De Stavola, Bianca
RO: University College London
Title: HOD1: Comparative Effectiveness Research using Observational Data: Methodological Developments and a Roadmap (CER-OBS)
Grant duration: 36
Provisional award: £582,118

The potential gains for enhancing comparative effectiveness research (CER) by exploiting linked health-related databases are indisputable. However, the potential pitfalls that may arise from not properly accounting for the administrative nature of this information have fuelled a debate on its utility. A promising approach that addresses (some of) these concerns advocates the implementation of trial design principles when exploiting observational data in CER. It consists of emulating the trial that would be designed to study the effectiveness of a treatment by specifying the target population and target comparative measures, and then handling/analysing the observational data to replicate them. There are still several unmet challenges for a robust adoption of this approach, however:

Study design:
Erroneous decisions at any step of the construction of the emulated trial may affect the robustness of the reported evidence. Awareness of potential methodological pitfalls is essential for the interpretation and delivery of evidence.

Data quality:
The coarseness often affecting observational data and the likely dependence of the timing of the observations on factors related to the disease evolution, impact on the robustness of the adopted estimation approach.

Estimation:
Most CER involves treatments sustained over time and requires implementing g-methods for estimation. G-estimation of structural nested models is the most flexible, particularly for dealing with multiple confounders and/or time-points, but has not been fully exploited in applications, nor extended to deal with data coarseness and dependent follow-up.

Given these challenges, this application aims to:
A) Create a roadmap for the assessment and robust delivery of evidence that adopts the "emulate the target trial" approach.
B) Extend g-estimation to deal with data coarseness and dependent follow-up.
C) Use clinically relevant exemplars to illustrate both approach and methodological developments.

Grant ref: MR/R025223/1

PI: Dias, Sofia
RO: University of Bristol
Title: HOD1: Inferring relative treatment effects from combined randomised and observational data
Grant duration: 36
Provisional award: £737,795

Randomised controlled trial (RCT) evidence is the gold-standard to estimate relative treatment effects. Network meta-analysis (MA) is used to pool evidence from RCTs to compare multiple treatments. There is a trend towards appraising new health technologies with limited or single arm evidence, which requires adjustment methods that make strong assumptions.

When RCT evidence is limited, as is increasingly the case, observational data is a potential supplementary source of
evidence. We will develop methods and guidance on different ways in which observational evidence can be used in
decision making in five related work packages (WP):

WP1: Development of methods to adjust effect estimates for imbalances in effect modifiers in disconnected networks of
RCT, including single-arm studies. Methods to estimate the degree of error in the estimates obtained will also be
developed.

WP2: We will investigate the properties of bias adjustment methods proposed in the literature in terms of their potential to estimate and adjust for bias and reduce decision uncertainty, to determine which method is likely to work best for different kinds of RCT and observational data structures.

WP3: Real world linked patient level data offers an opportunity to explore the effect of treatments in patients who may be
under-represented in RCT, but are subject to selection effects and confounding. We will explore propensity scoring,
Instrumental Variable and Structural Equation Modelling for the estimation of treatment effects from such data. Simulation studies will be carried out to compare the performance of these methods.

WP4: The use of registry data, adjusted for population differences and selection bias, to enhance randomised trial evidence in the context of managed entry of new pharmaceuticals will be explored.

WP5: Methods will be developed to explore how biased would the evidence (including observational evidence) have to be before it changed the decision.

Please note, formal acceptance of the above awards is pending, and summaries are provided for information only and may be subject to change.