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Common themes in HEAPs in CVD Prevention: towards standardisation

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Credentials

- Economic analyses alongside large pragmatic/streamlined cardiovascular disease prevention RCTs
- Lipid modification
  - HPS: n=20,536; UK; Statin vs Placebo
  - SHARP: n=9,270; Multinational; Statin/Ezetimibe vs Placebo
  - THRIVE: 25,673; Multinational; Niacin/Laropiprant vs Placebo
- Blood-pressure lowering
  - EUROPA: n=12,218; Multinational; ACE I vs Placebo
- HEAP approach has evolved

General principles of HEA

- RCT data to inform HE
  - Focus on main drivers on differences in health outcomes, resource use and cost
  - Minimise data collection to not impede on recruitment and retention of study participants
  - Consider whether the RCT is the best source of data needed
  - Organise data collection in a way to minimise missing data and maximise data quality
- HE Analysis:
  - Closely based on RCT design: Intention-To-Treat principle
  - Consistent with main clinical analysis: driven by main Tx effects in RCT
  - **Inform decisions:** any important external factors need to be considered: e.g. Relevant alternative intervention; patient heterogeneity

HEAP: Perspective and Time Horizon

- Perspective
  - So far: Health services perspective
    - UK and US;
- Time horizon
  - Within trial: focus on major cardiovascular events avoided
    - Robust but usually not considered sufficiently informative
  - Lifetime/ long-term: focus on life years and quality-adjusted life-years
    - Requires long-term extrapolation!

HEAP: Outcomes data

- Health outcomes:
  - Morbidity/ Mortality: all morbidity not just first events.
  - Quality of life (EQ-5D)
- Resource use
  - Focus on main resource use elements:
    - Tx use/costs: both trial arms
    - Hospital care use- inpatient and outpatient care;
    - Other important resources?

HEAP: data collection

- Electronic data collection with quality assuring mechanisms
  - Pre-specifying analysis helps secure better quality data!
  - Usually require data to be collected by study personnel during visits
  - Electronic data capture : participants filling forms electronically
- Electronic patient records increasingly considered in study design
  - Not yet the norm but progress made even in multi-national trials
- Patient –filled paper questionnaires- largely impractical in the context of large pragmatic trials
- External data could supplement study data

HEAP Analysis I

- Analysis of resource use/ costs
  - Costing Tx use- compliance data but also likely drug waste
  - Costing healthcare use- use accepted methods (e.g. reference costs in UK)
  - We consider excluding from analysis categories of resource use for which no prior hypothesis and no Tx effect shown in RCT (e.g. non-CVD hospital care)
  - We consider using differently resource use data from countries where healthcare use differs from target perspective
- Analysis of health outcomes
  - EQ-5D tariff for the target perspective applied to multinational data; sensitivity analysis with different valuation set/s

HEAP Analysis II: Within-trial cost-effectiveness

- Effect of allocation to Tx on morbidity, resource use and costs during follow-up in the study
- *Outcome measure*: Incremental cost per Major Vascular Event avoided
- Missing data: simple and robust method of imputation
- Focus on:
  - Heterogeneity of effect across participants: e.g. by cardiovascular disease risk
  - Compliance with treatment

Robust analysis but of policy interest only if Tx dominates/ is dominated!

HEAP Analysis III: Lifetime cost-effectiveness

- Outcome measure: LYs, QALYs gained with Tx
- An extrapolation model
  - Detail of model difficult to fully pre-specify in HEAP unless an external/previously developed model used
  - Specify the general modelling framework:
    - How will model be developed [using RCT/external data]?
    - Type of model: e.g. a Markov decision analytic model, cycle length
    - What are the main drivers of future morbidity, mortality and healthcare use (e.g. model states)?
      - Key/major disease events including those affected by Tx
    - Sources of QoL utilities and costs related to model states
    - Considerations for model validation: internal , external

HEAP Analysis IV: Event-driven extrapolation in CVD prevention

- Key/major disease events [including events affected by Tx] in the backbone of the extrapolation
  - ➢ Earlier events/patient characteristics determine subsequent events
- QoL related to key/major disease events
  - ➢ Regression framework
- Healthcare costs related to key/major disease events
  - ➢ Regression framework
- Patient heterogeneity implemented across elements of the evaluative framework
- **Effects of Tx on morbidity, QoL, healthcare costs propagated through Tx effect on primary/key endpoints in RCT**

HEAP Analysis V

- Present CE results for categories of participant by CVD risk and age
- Include **sensitivity analyses**, including:
  - Tx price
  - Duration of Tx effects
  - Patterns of compliance with Tx, including full compliance
- Evaluate statistical uncertainty in results due to uncertainty in parameters in the evaluative framework/s
  - Bootstrap approach

Do we follow our HEAPs?

- Largely "Yes"
  - HEAPs are not very detailed
- Principal deviations due to:
  - Tx intervention not effective in RCT:
    - CE analysis not performed
    - No extrapolation framework developed
  - A further intervention/comparator: generic intervention as an alternative to trialled Tx!

Some concluding remarks

- Usefulness of HEAPs
  - Help to frame HE questions and focus on major things
  - Inform data collection so important gaps in data avoided
- Do HEAPs need to be finalised prior to RCT initiation/ data unblinding?
  - Possibly not if HE analysis follows good practice to minimise biases: e.g. ITT RCT Tx effects on primary/key outcomes drive HE analysis;
  - HE extrapolation frameworks could be validated using the RCT data;
  - HE analysis need to incorporate all relevant factors/evidence at time of analysis, including those emerging post RCT completion.