Please see below for a link to the webinar recording for the Trials Methodology Research Partnership:

**Documenting trial methods: the HEAP**

*Jo Thorn (University of Bristol)*

14 October 2021

On behalf of the MRC Hubs for Trials Methodology Research

The slides are also available below.

For any queries, please contact uktmn@nottingham.ac.uk

[https://www.youtube.com/watch?v=yntaJnXqZzA](https://www.youtube.com/watch?v=yntaJnXqZzA)
Documenting trial methods - the Health Economics Analysis Plan (HEAP)

Jo Thorn, University of Bristol, 14 October 2021
• Jo Thorn, Will Hollingworth, Sian Noble, Charlotte Davies, Sara Brookes: University of Bristol
• Dyfrig Hughes, Colin Ridyard: Bangor University
• Sarah Wordsworth, Boby Mihaylova, Melina Dritsaki: University of Oxford
• Ed Wilson, Tracey Sach: University East Anglia
• Stavros Petrou: Warwick University
• Ewan Gray: University of Edinburgh
HEAPs – what do we mean?

“...document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data”

ICH Topic E 9 Statistical Principles for Clinical Trials. NOTE FOR GUIDANCE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS.
HEAPs – what do we mean?

“...document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the economic analysis of the primary and secondary variables and other data”

ICH Topic E 9 Statistical Principles for Clinical Trials. NOTE FOR GUIDANCE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS.
Purpose of SAP/HEAP

• Reduce reporting bias
  – Choice of outcome measures appearing in final report
  – Inclusion/exclusion of outliers
  – Nature of analyses applied
Workshop

• Collate information on the current state of play
• Provide an environment in which health economists could start to debate the issues
• Feedback
  – HEAPs have some merits
  – Substantial appetite for guidance
Overall, the economics protocol and analysis plan should cover the following issues relating to study design, data collection, and data analysis, providing justifications for the analytic decisions made:

- The study’s objective, question, and perspective;
- The principal hypothesis to be tested;
- The form of economic analysis;
- The comparators to be included;
- The range of costs to be considered in the study (including explanations for the exclusion of any resource items);
- The assessment of quality-of-life data (or an explanation of why it is excluded);
- The data to be collected and sources of data;
- The length of follow-up;
- The statistical tests to be conducted;
- The methods for dealing with missing data and study withdrawals; and
- The methods for synthesis of resource use, and clinical and quality of life information.

It has been argued that it may not be possible to determine the appropriate analytical framework for an evaluation until after all data are available (4). However, an analysis plan should at least identify the criteria by which an analytical framework will be chosen.

Guiding Principles

The analysis of economic measures should be guided by a data analysis plan. A prespecified plan is particularly important if formal tests of hypotheses are to be performed. Any tests of hypotheses that are not specified within the plan should be reported as exploratory. The plan should specify whether generalized linear model, least squares regression, or other multivariable analysis will be used to improve precision and to adjust for treatment group imbalances. The plan should also identify any selected subgroups and state the type of analysis, for example, intention-to-treat or modified intention-to-treat, that will be conducted. The plan should be finalized before trial data are unblinded; publication of the analysis plan before the completion of the trial is a best practice [87–89].

Keywords: clinical trial, cost-effectiveness, economic, guidelines.

Copyright © 2015, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc.
### Pre-Analysis Plan Checklist

<table>
<thead>
<tr>
<th>Item</th>
<th>Brief description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome variable</td>
<td>The key variable of interest for the study. If multiple variables are to be examined, one should know how the multiple hypothesis testing will be done.</td>
</tr>
<tr>
<td>Secondary outcome variable(s)</td>
<td>Additional variables of interest to be examined.</td>
</tr>
<tr>
<td>Variable definitions</td>
<td>Precise variable definitions that specify how the raw data will be transformed into the actual variables to be used for analysis.</td>
</tr>
<tr>
<td>Inclusion/Exclusion rules</td>
<td>Rules for including or excluding observations, and procedures for dealing with missing data.</td>
</tr>
<tr>
<td>Statistical model specification</td>
<td>Specification of the precise statistical model to be used, hypothesis tests to be run.</td>
</tr>
<tr>
<td>Covariates</td>
<td>List of any covariates to be included in analysis.</td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td>Description of any heterogeneity analysis to be performed on the data.</td>
</tr>
<tr>
<td>Other issues</td>
<td>Other issues include data monitoring plans, stopping rules, and interim looks at the data.</td>
</tr>
</tbody>
</table>

Olken (2015) *J. Econ. Perspectives* 29(3)
Clinical trials units

- Approx. 30% CTUs use a HEAP
- No consistency in approach

Appendix 4 Health economic analysis plan

THE UNIVERSITY OF LIVERPOOL

SLEEPS (Safety profile, Efficacy and Equivalence in Paediatric Intensive care Sedation) Trial

Health Economics Analysis Plan

Angela Boland / Stavros Petrou

May 2013
Economic analyses

Economic analysis of trial treatment effects will involve a within-trial evaluation of cost effectiveness integrated into a decision-analytic model of longer run costs and health effects. The within-trial analysis will be conducted on an intention-to-treat basis. The primary health endpoints will be survival times adjusted for quality of life. A standard multiplicative model will be used to estimate quality adjusted life years (QALYs) by the area under linear interpolation of the EQ-5D-3L index trajectory for each individual patient using survival times, the EQ-5D-3L index score at 6 months and a modeled baseline EQ-5D-3L index score. We will assess robustness using probabilistic sensitivity analysis of the parameters used to generate the short-run QALY estimates.

A NHS perspective will be adopted for assessing resource use and costs. Patient-specific hospital resource use will be measured using the duration of stay for the index episode following randomization. The net direct medical cost will include the hospital stay, converted into cost estimates using NHS per diem hospital costs, a cost estimate of IPC capital/equipment (and staffing implications) and the averted costs arising from the effects of IPC on expected DVT/PE incidence. Trial centre or region-specific per diem hospital costs will be based on NHS reference costs in England and cost information for NHS Scotland derived from the Scottish Health Service.
Economic analysis plan

Health economic objectives (secondary)

We will take both a health service perspective in the economic evaluation intervention will be calculated by staff time needed for training, support of the educational session and travel heads and capital costs. The cost will be calculated by the above information. The Client Service Receipt adapted and used to record the use also unpaid carer time and time lost by user data will be combined with reimbursement information [33]. Lost employment by combining lost work time rates. Health-care and societal costs compared between the two arms model with baseline costs controlled for often skewed, and we will use bootstrapping 95% confidence intervals around To assess cost-effectiveness, we will use data for the primary outcome measure at 12 months. Cost utility will be assessed by combining costs with quality-adjusted life years (QALYs), which will be generated from the European Quality of Life-5 Dimensions (EQ-5D) questionnaire. If the intervention outcomes and lower costs, it will be "dominant". If it results in better outcomes, incremental cost-effectiveness will be used to show the extra cost incurred by the treatment arm.

Economic measures

Client Services Receipt Inventory: This will record contacts with health-care services at baseline and over the follow-up. It includes hospital admissions, contact with primary and community care, and receipt of care from family and friends. In addition, it includes lost work time.

EQ-5D: QALYs will be calculated from the EQ-5D health state classification instrument. This covers five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, the respondent chooses one of five levels of functioning, from good to poor. The five levels for each of the five domains are used to define unique health states to which a pre-estimated “utility” value will be attached.
SAPs guidance

- Little guidance found (ICH E9)
- Delphi survey for content (61 items)
- Minimum content; not standalone
- Consensus OUT: “details of any other analyses to be conducted by others e.g. Health Economics etc”

Delphi survey

• Consensus technique
  – Experts asked to provide judgment on items
  – Iterative process with feedback
  – Anonymity maintained
  – Wide geographical area
Methods

- Extracted potential items from HEAPs
  - \( N = 72 \) after deduplication
- Developed electronic Delphi survey

| Monitoring collection of health economic data | 28 | Outline how the health economic data collected will be monitored | e.g. training will be provided to individuals responsible for administering the HE questionnaires. The trial HE(s) will work closely with the trial team throughout the data collection period. Data collection forms will be assessed throughout the trial period to monitor quality of the data and amend any forms or procedures if necessary |
Structure of HEAP list

List of items divided into 8 main sections (72 items in total)

- Section 1: Administrative Information (16 items)
- Section 2: Introduction and Background (7 items)
- Section 3: Economic Approach/Overview (4 items)
- Section 4: Economic Data Collection & Management (12 items)
- Section 5: Economic Data Analysis (16 items)
- Section 6: Modelling & Value of Information analyses (9 items)
- Section 7: Reporting/Publishing (3 items)
- Section 8: References and Appendices (5 items)
- Recruited 62 participants in round 1
- Asked to rate each item 1-9

<table>
<thead>
<tr>
<th>Consensus classification</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus in</td>
<td>Consensus that component should be included in the HEAP</td>
<td>50% (R1) or 70% (R2) or more participants scoring as 7 to 9 AND &lt;15% participants scoring as 1 to 3</td>
</tr>
<tr>
<td>Consensus out</td>
<td>Consensus that component should not be included in the HEAP</td>
<td>50% (R1) or 70% (R2) or more participants scoring as 1 to 3 AND &lt;15% of participants scoring as 7 to 9</td>
</tr>
<tr>
<td>No consensus</td>
<td>Uncertainty about importance of component</td>
<td>Anything else</td>
</tr>
</tbody>
</table>
Round 2 evolved with feedback

- 48 responses (77.4%)
- 53 items ‘consensus in’, 19 no consensus
Final item selection meeting

- 8 team members, 2 participants, 2 CTU representatives, Delphi co-ordinator
- 9 voters, electronic voting system
- 58 items on final list, with 9 on an ‘optional’ list
## Results from Delphi Survey

<table>
<thead>
<tr>
<th>Item</th>
<th>ROUND 1 Median score</th>
<th>ROUND 1 Item IN/OUT or NO CONSENSUS</th>
<th>ROUND 2 Median score</th>
<th>ROUND 2 Number (%) rated 7 to 9</th>
<th>ROUND 2 Number (%) rated 1 to 3</th>
<th>ROUND 2 Item IN/OUT or NO CONSENSUS</th>
<th>Item status after final voting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>8</td>
<td>IN</td>
<td>8</td>
<td>39 (81.3)</td>
<td>3 (6.3)</td>
<td>IN</td>
<td>IN</td>
</tr>
<tr>
<td>Trial registration number</td>
<td>8</td>
<td>IN</td>
<td>8</td>
<td>42 (87.5)</td>
<td>1 (2.1)</td>
<td>IN</td>
<td>IN</td>
</tr>
<tr>
<td>Source of funding</td>
<td>8</td>
<td>IN</td>
<td>8</td>
<td>40 (83.3)</td>
<td>2 (4.2)</td>
<td>IN</td>
<td>IN</td>
</tr>
<tr>
<td>Purpose of HEAP</td>
<td>8</td>
<td>IN</td>
<td>8</td>
<td>37 (77.1)</td>
<td>2 (4.2)</td>
<td>IN</td>
<td>IN</td>
</tr>
<tr>
<td>Sponsor approval</td>
<td>6.5</td>
<td>NO CON</td>
<td>6</td>
<td>14 (29.2)</td>
<td>5 (10.4)</td>
<td>NO CON</td>
<td>OUT</td>
</tr>
<tr>
<td>Trial protocol version</td>
<td>7</td>
<td>IN</td>
<td>7</td>
<td>37 (77.1)</td>
<td>1 (2.1)</td>
<td>IN</td>
<td>IN</td>
</tr>
<tr>
<td>Trial statistical analysis plan (SAP) version</td>
<td>7</td>
<td>IN</td>
<td>7</td>
<td>34 (70.8)</td>
<td>1 (2.1)</td>
<td>IN</td>
<td>IN</td>
</tr>
<tr>
<td>Trial HEAP version</td>
<td>8</td>
<td>IN</td>
<td>8</td>
<td>42 (87.5)</td>
<td>1 (2.1)</td>
<td>IN</td>
<td>IN</td>
</tr>
</tbody>
</table>
### Section 5: Economic data analysis

<table>
<thead>
<tr>
<th>5.1</th>
<th>Analysis population</th>
<th>Outline the analysis population that will be used in the economic base-case analysis (such as intention to treat, per protocol)</th>
<th>The full analysis set will include all randomised participants, which is in accordance with the “intention to treat” (ITT) principle. A per protocol set will include all participants in the full analysis set who are deemed to have no major protocol violations (e.g. patient not receiving any of the intended intervention).</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2</td>
<td>Timing of analyses</td>
<td>Describe the timing of all planned analyses (e.g. interim and final analyses)</td>
<td>The primary (“final”) analysis will be conducted once all patients have been followed for two years after the first dose of [trial drug], although an interim analysis will be conducted on year 1 data once all patients have been followed for one year. The interim analysis will take a one-year time horizon and use only data collected in patients’ first year of follow-up, with no extrapolation. The final analysis will include a within-trial analysis, taking a two-year time horizon and extrapolating beyond the end of the trial.</td>
</tr>
<tr>
<td>5.3</td>
<td>Discount rates for costs and benefits</td>
<td>Detail the source of, and justification for, discount rates used for costs and benefits</td>
<td>Costs and benefits will be discounted at 3.5% p.a. as recommended by NICE.</td>
</tr>
<tr>
<td>5.4</td>
<td>Cost-effectiveness threshold(s)</td>
<td>Detail the cost-effectiveness threshold(s) to be used in analysis/interpretation</td>
<td>The estimated mean QALYs and costs associated with each treatment option will be combined with a feasible range of values for decision makers’ willingness-to-pay (WTP), to obtain the distribution of net benefits at different levels of WTP. The primary economic analysis will use a cost-effectiveness threshold of £20,000 per QALY.</td>
</tr>
<tr>
<td>5.5</td>
<td>Statistical decision rule(s)</td>
<td>Describe how inference will be drawn (e.g. significance level, confidence intervals or mean net benefit)</td>
<td>Mean differences in costs, QALYs and net benefits between the treatment groups will be estimated with associated 95% confidence intervals.</td>
</tr>
</tbody>
</table>
HEAPs are a help...

- Reduction of reporting bias
- Can anticipate problems before analysis pressure is on
- Defining variables can secure better quality data
- Can facilitate communication and good habits
- Protects junior staff from overzealous research partners
- Robust rebuttal to reviewer requests
- Staff turnover
- Methods section already written!
HEAPs are a hindrance...

- Bureaucratic burden on a small workforce
- Added complexity – oversight
- Loss of potentially useful post hoc analyses
- Impossible to predict all data issues
- Potential loss of useful new methodology
Is there a problem?

• “Even researchers who have the noblest of intentions may end up succumbing to the same sorts of biases when... ...[making] sense of a complex set of results” (Olken, B. J. Econ. Perspectives 29(3) p62)

• Perhaps being seen to be above board is just as important

APPROVED
Will standardised HEAPs improve the quality of economic evaluations alongside RCTs?
Issues

• When is it acceptable to deviate from the HEAP?

• At what point (if ever) should a HEAP be considered final or signed off?

• Should HEAPs be published?

• Are there any circumstances in which a HEAP could be considered unnecessary?
“I am opposed to the laying down of rules or conditions to be observed in the construction of bridges lest the progress of improvement tomorrow might be embarrassed or shackled by recording or registering as law the prejudices or errors of today.”

Isambard Kingdom Brunel
1806–1859
Acknowledgments

• MRC Network of Hubs for Trials Methodology Research (MR/L004933/1-N65) (www.methodologyhubs.mrc.ac.uk)

• ConDuCT-II Hub for Trials Methodology Research (https://www.bristol.ac.uk/population-health-sciences/centres/conduct2/)
joanna.thorn@bristol.ac.uk

ConDuCT-II Hub for Trials Methodology Research
(https://www.bristol.ac.uk/population-health-sciences/centres/conduct2/)