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

Documenting trial methods - the Health Economics Analysis Plan (HEAP)

Jo Thorn, University of Bristol, 14 October 2021

PRIFYSGOL BANGOR UNIVERSITY

UNIVERSITY OF OXFORD

University of BRISTOL

MRC Hubs for Trials Methodology Research

ConDuCT-II Hub

- **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?

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"…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?

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"…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

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

Workshop

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- 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

HEAPs guidance (I)

International Journal of Technology Assessment in Health Care, 14:1 (1998), 135–144.

TRIALS AN

Emerging Issu
Evaluations Al

Douglas Coyle
University of Ottawa

Linda Davies
Michael F. Drumm
University of York

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.

HEAPs guidance (II)

Volume 8 • Number 5 • 2005
VALUE IN HEALTH

VALUE IN HEALTH 18 (2015) 161–172

Good Research Practices for Cost-
Alongside Cli
Force Report

Analysis

Scott Ramsey, MD, Phl
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Inc, Blue Bell, PA, USA; [8]Unive
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CrossMark

ABSTRACT

Objectives: A growing nu
als include economic end
tion in methodology and
International Society for
comes Research (ISPOR)
Good Research Practices:
Cost-Effectiveness Analys
guidance document for des
ing cost-effectiveness analy
ical trials.

Methods: Task force coch
Board of Directors. Coch
participate. Panel member
academia, the pharmaceut
ance plans. An outline and
panel were presented at
European ISPOR meeting
was then submitted to a r
comment.

Results: The report addresses issues related to trial design, selecting data elements, database design and man-

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].

validity. In 2005, ISPOR published the Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force report. ISPOR initiated an update of the report in 2014 to include the methodological developments over the last 9 years. This report provides updated recommendations reflecting advances in several areas related to trial design, selecting data elements, database

porting of results. Task force
ned to evaluate effectiveness
uld include clinical outcome
source use and health state
Collection of economic data
ly. An incremental analysis
-to-treat approach, comple-
Uncertainty should be char-
established standards for
analyses. Economic studies
her evaluations (e.g., model-
ing studies) as information for decision makers who consider evidence of economic value along with clinical efficacy when making resource allocation decisions.

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

HEAPs guidance (III)

Pre-Analysis Plan Checklist

Item	*Brief description*
Primary outcome variable	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.
Secondary outcome variable(s)	Additional variables of interest to be examined.
Variable definitions	Precise variable definitions that specify how the raw data will be transformed into the actual variables to be used for analysis.
Inclusion/Exclusion rules	Rules for including or excluding observations, and procedures for dealing with missing data.
Statistical model specification	Specification of the precise statistical model to be used, hypothesis tests to be run.
Covariates	List of any covariates to be included in analysis.
Subgroup analysis	Description of any heterogeneity analysis to be performed on the data.
Other issues	Other issues include data monitoring plans, stopping rules, and interim looks at the data.

Olken (2015) *J. Econ. Perspectives* 29(3)

Clinical trials units

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

Dritsaki M, Gray A, Petrou S, Dutton S, Lamb SE and Thorn JC (2018) 'Current UK Practices on Health Economics Analysis Plans (HEAPs): Are We Using Heaps of Them?' *PharmacoEconomics* **36** 253-257

Published HEAPs

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DOI: 10.3310/hta18710 HEALTH TECHNOLOGY ASSESSMENT 2014 VOL. 18 NO. 71

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

Published SAP/HEAP

Dennis *et al. Trials* 2013, 14
http://www.trialsjournal.com

TRIALS

UPDATE

Open Access

Does inte … reduce
the risk o … sis? The
CLOTS 3 t …

Martin Dennis[1*], Peter …
Collaboration

… Trials

Abstract

Background: Venous … The CLOTS 3
trial aims to determin … tent pneumatic
compression (IPC) in … (DVT).

Methods/Design: Th … ation

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 end-points 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

Published SAP/HEAP/QAP

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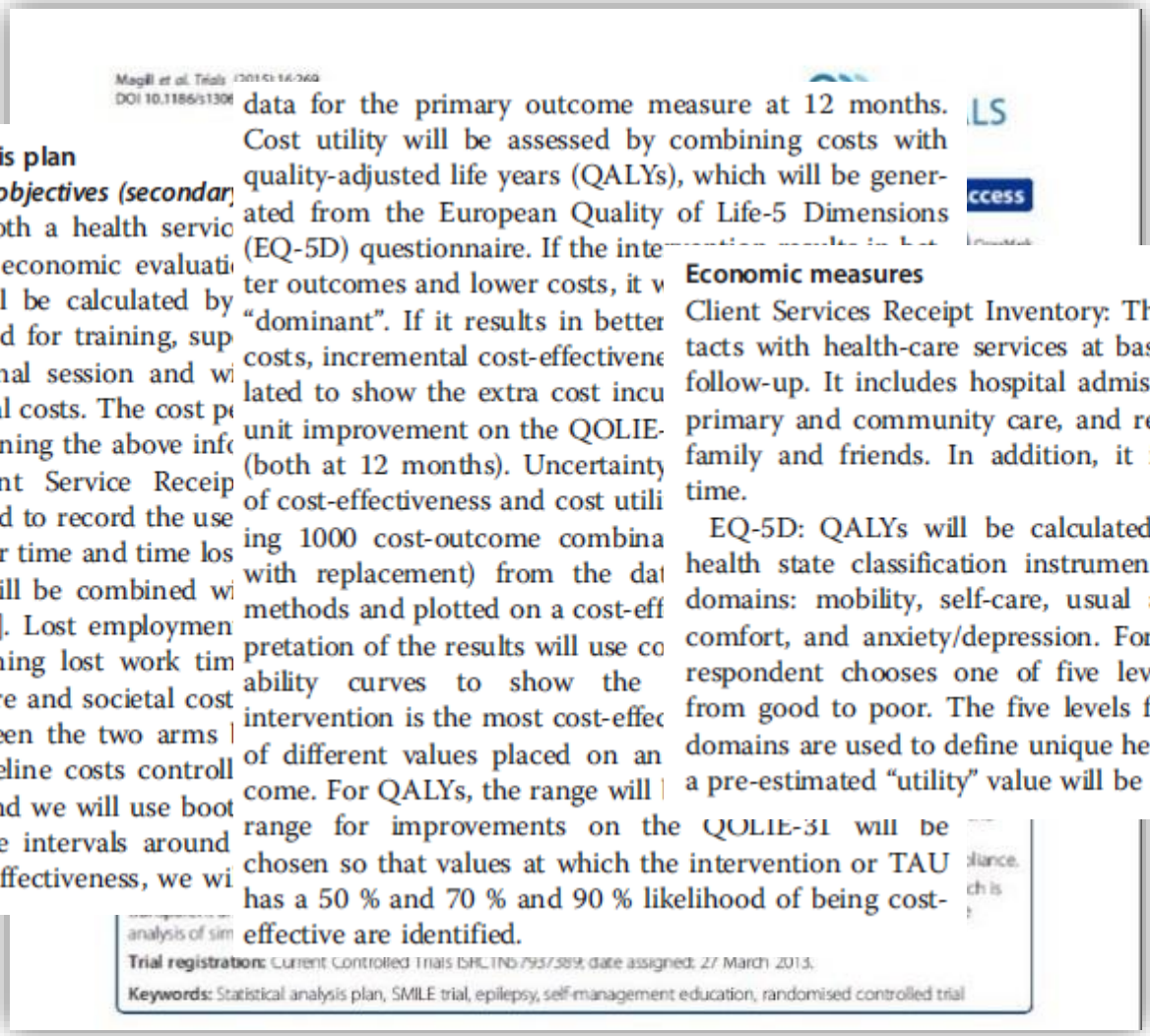

Magill et al. Trials (2015) 16:269
DOI 10.1186/s13063

Economic analysis plan

Heath economic objectives (secondary

We will take both a health servic
spective in the economic evaluati
intervention will be calculated by
staff time needed for training, sup
of the educational session and wi
heads and capital costs. The cost pe
mated by combining the above info
data. The Client Service Receip
adapted and used to record the use
also unpaid carer time and time los
vice use data will be combined wi
information [33]. Lost employmen
lated by combining lost work tim
rates. Health-care and societal cost
compared between the two arms
model with baseline costs controll
often skewed, and we will use boot
95 % confidence intervals around
To assess cost-effectiveness, we wi

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 inte
ter outcomes and lower costs, it w
"dominant". If it results in better
costs, incremental cost-effectivene
lated to show the extra cost incu
unit improvement on the QOLIE-
(both at 12 months). Uncertainty
of cost-effectiveness and cost utili
ing 1000 cost-outcome combina
with replacement) from the dat
methods and plotted on a cost-eff
pretation of the results will use co
ability curves to show the
intervention is the most cost-effec
of different values placed on an
come. For QALYs, the range will
range for improvements on the QOLIE-31 will be chosen so that values at which the intervention or TAU has a 50 % and 70 % and 90 % likelihood of being cost-effective are identified.

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.

analysis of sim

Trial registration: Current Controlled Trials ISRCTN79573859; date assigned: 27 March 2013.

Keywords: Statistical analysis plan, SMILE trial, epilepsy, self-management education, randomised controlled trial

SAPs guidance

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- 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*”

Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. Jama. 2017;318(23):2337-43.

Delphi survey

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

Methods

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- 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

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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)

Items

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- Recruited 62 participants in round 1
- Asked to rate each item 1-9

Consensus classification	Description	Definition
Consensus in	Consensus that component should be included in the HEAP	50% (R1) or 70% (R2) or more participants scoring as 7 to 9 AND <15% participants scoring as 1 to 3
Consensus out	Consensus that component should not be included in the HEAP	50% (R1) or 70% (R2) or more participants scoring as 1 to 3 AND <15% of participants scoring as 7 to 9
No consensus	Uncertainty about importance of component	Anything else

Round 2

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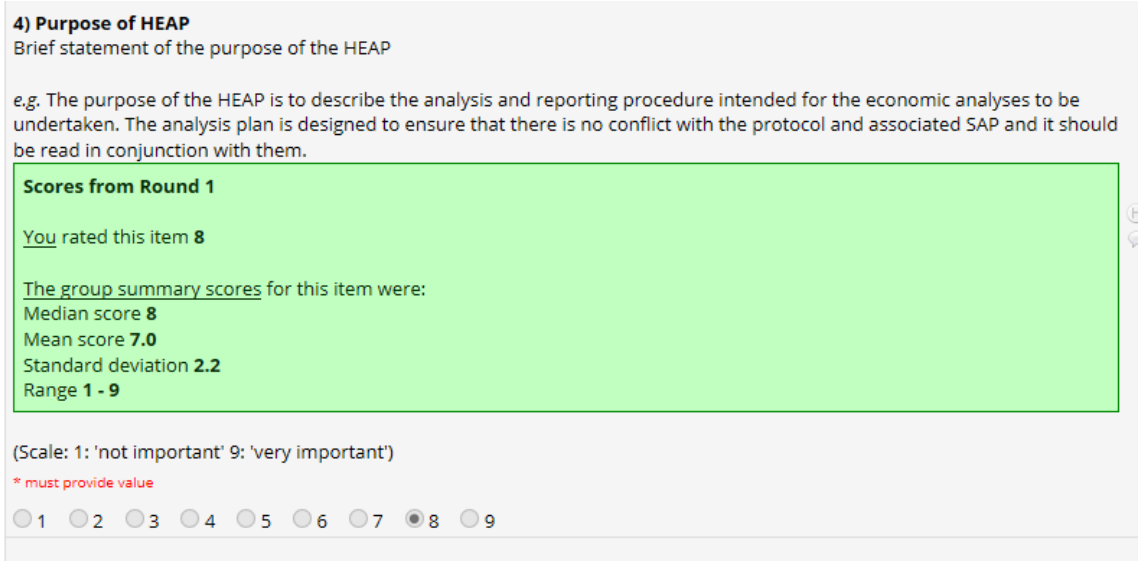
- Round 2 developed with feedback



4) Purpose of HEAP
Brief statement of the purpose of the HEAP

e.g. The purpose of the HEAP is to describe the analysis and reporting procedure intended for the economic analyses to be undertaken. The analysis plan is designed to ensure that there is no conflict with the protocol and associated SAP and it should be read in conjunction with them.

Scores from Round 1

You rated this item **8**

The group summary scores for this item were:
Median score **8**
Mean score **7.0**
Standard deviation **2.2**
Range **1 - 9**

(Scale: 1: 'not important' 9: 'very important')

* must provide value

○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ◉ 8 ○ 9

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

Final item selection meeting

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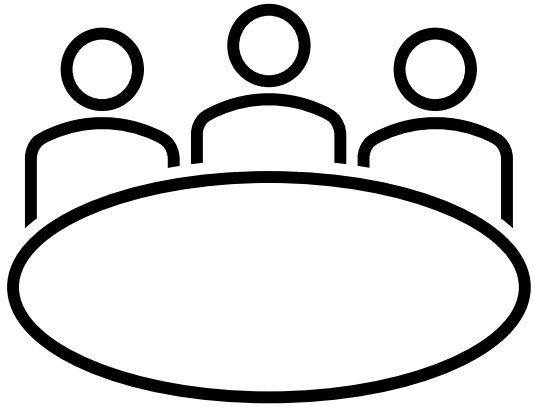
- 8 team members, 2 participants, 2 CTU representatives, Delphi co-ordinator
- 9 voters, electronic voting system
- 58 items on final list, with 9 on an ‘optional’ list



Results from Delphi Survey

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

Template (in supplementary materials)

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Section 5: Economic data analysis			
5.1	Analysis population	Outline the analysis population that will be used in the economic base-case analysis (such as intention to treat, per protocol)	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).
5.2	Timing of analyses	Describe the timing of all planned analyses (e.g. interim and final analyses)	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.
5.3	Discount rates for costs and benefits	Detail the source of, and justification for, discount rates used for costs and benefits	Costs and benefits will be discounted at 3.5% p.a. as recommended by NICE.
5.4	Cost-effectiveness threshold(s)	Detail the cost-effectiveness threshold(s) to be used in analysis/interpretation	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 (λ), to obtain the distribution of net benefits at different levels of λ. The primary economic analysis will use a cost-effectiveness threshold of £20,000 per QALY.
5.5	Statistical decision rule(s)	Describe how inference will be drawn (e.g. significance level, confidence intervals or mean net benefit)	Mean differences in costs, QALYs and net benefits between the treatment groups will be estimated with associated 95% confidence intervals.

HEAPs are a help…

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- 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…

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- 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

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

ELSEVIER

Value in Health
Volume 24, Issue 4, April 2021, Pages 539-547

Methodology

Content of Health Economics Analysis Plans (HEAPs) for Trial-Based Economic Evaluations: Expert Delphi Consensus Survey

Joanna C. Thorn PhD [1] * ✉, Charlotte F. Davies PhD [1, *], Sara T. Brookes PhD [1], Sian M. Noble PhD [1], Melina Dritsaki PhD [2], Ewan Gray PhD [3], Dyfrig A. Hughes PhD [4], Borislava Mihaylova DPhil [5, 6, 7], Stavros Petrou PhD [8], Colin Ridyard PhD [4], Tracey Sach PhD [9], Edward C.F. Wilson PhD [9], Sarah Wordsworth PhD [5, 7], William Hollingworth PhD [1]

Thorn JC, Davies CF, Brookes ST, Noble SM, Dritsaki M, Gray E, Hughes DA, Mihaylova B, Petrou S, Ridyard C, Sach T, Wilson ECF, Wordsworth S and Hollingworth W (2021) 'Content of Health Economics Analysis Plans (HEAPs) for trial-based economic evaluations: expert Delphi consensus survey' *Value in Health* **24**(4) 539–47 doi: 10.1016/j.jval.2020.10.002

Acknowledgments

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- 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/)

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