Institution: University of Liverpool

Unit of Assessment: 10 – Mathematical Sciences

Title of case study: The COMET (**C**ore **O**utcome **M**easures in **E**ffectiveness **T**rials) Initiative establishes international standard in clinical trials policy, guidance and patient participation

Period when the underpinning research was undertaken: January 2000 – June 2014

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof Paula R. Williamson	Senior Lecturer/Reader/Professor of Medical Statistics	1996-present
Prof E.Victor Flynn	Professor of Pure Mathematics	1994-2005
Dr Seokyung Hahn	Senior Research Assistant (Statistics)	1998-2000

Period when the claimed impact occurred: August 2013 – October 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Worldwide clinical trials are the mechanism by which the safety and effectiveness of medicines and interventions are assessed. Mathematicians from the University of Liverpool discovered a systemic problem with outcome selection and reporting bias across the entire clinical trials sector and established the COMET Initiative (**C**ore **O**utcome **M**easures in **E**ffectiveness **T**rials) in response, generating key policy and societal impacts. COMET is now the international standard for harmonising outcomes - making decisions about treatments more robust by ensuring that effectiveness data can be compared and combined, and making trials relevant to patients. COMET has transformed patient participation in outcome-setting during the REF period from 16% to 93%. Endorsed by the European Medicines Agency (EMA), COMET is being used by ten healthcare decision-making organisations including guideline developers such as NICE, and trial funders including the NIHR and the pharmaceutical industry.

2. Underpinning research

Results from clinical trials guide treatment decisions for patients and health professionals and are needed for licensing new medicines. Clinical trials are the gold standard for evaluating treatments such as drugs, procedures or psychological interventions, by comparing relative effects on health outcomes. 'Outcomes' are what is measured in participants to assess the effect of an intervention. Thousands of different outcomes may be identified across many different diseases and conditions. University of Liverpool mathematicians retrospectively analysed clinical trial data and uncovered i) a lack of consistency in outcomes selected for measurement across trials for particular conditions, and ii) subsequent selective reporting of outcome results in a biased way. These two issues make comparing and combining trial data difficult.

The rigorous study of and statistical adjustment for the detrimental effects of poor outcome selection and reporting bias within individual clinical trials originated in 2000 by Prof Paula Williamson, then a senior lecturer in the Division of Statistics and Operational Research, Department of Mathematical Sciences at the University of Liverpool. Prof Williamson initiated work with Prof Jane Hutton (Newcastle University) to establish the potential consequences of selective outcome reporting bias in clinical trials and to propose statistical methods to assess the robustness of a trial to this problem **[3.1]**. Prof Williamson also investigated this issue of within-study selective reporting bias more generally at the time, recruiting statistician Dr Seokyung Hahn to Liverpool to work with her and Liverpool's pure mathematician E. Victor Flynn and Cochrane Editor Prof Paul Garner (Liverpool School of Tropical Medicine) on the selective

reporting of patient subgroup analysis within clinical studies **[3.2]**. Researchers from this same group published the first cohort study to evaluate the extent of within-study selective reporting, identifying that the problem of reporting bias they had uncovered could be significant **[3.3]**.

In 2002, Prof Williamson established a new Centre for Medical Statistics and Health Evaluation (now the Department of Biostatistics) at Liverpool, with promotion to Reader and then Professor in 2005. Her continuing work in this centre provided empirical evidence for the widespread existence of outcome reporting bias specifically, estimating the prevalence and impact in systematic reviews and more recently developing preventative initiatives and statistical approaches to adjust for this bias. This whole corpus of research was based on the initial insights detailed in **[3.1-3]**. A small selection of the many publications arising from the initial research into these biases are listed below **[3.4, 3.5]**.

In summary, **references [3.1, 3.2, 3.4] represent the body of underpinning statistics research** that established the problem and potential consequences of outcome selection and reporting bias. **[3.3, 3.5]** represent research on the scale of the problem, with **[3.5]** cited in the New York Times as '*empirical evidence that the biases are widespread*' (Carroll, AE. *Congratulations. Your study went nowhere* New York Times, 24th Sep. 2018).

These findings motivated Prof Williamson to found the COMET Initiative (**C**ore **O**utcome **M**easures in **E**ffectiveness **T**rials), launched by the University of Liverpool in 2010 to improve the consistency of outcome selection and reporting across the whole clinical trials sector. In 2014 a Liverpool-led systematic review populated the COMET database with all available **C**ore **O**utcome **S**ets (COS) **[3.6]**. This has since been updated six times (annually) to ensure COMET remains current. COMET is a global first in bringing COS together, where each COS defines a minimum agreed set of outcomes that should be measured and reported in all clinical trials for a particular condition.

Prof Williamson was the overall Principal Investigator on grants from the MRC (MR/J004847/1 and MR/K025635/1) and the European Commission FP7 (305081) that funded the set up and establishment of COMET, totalling GBP2,891,413.

3. References to the research

3.1. Hutton JL and **Williamson PR**. (2000) Bias in meta-analysis due to outcome variable selection within studies. Applied Statistics, 49: 359-370. doi:10.1111/1467-9876.00197

3.2. Hahn S, Williamson PR, Hutton JL, Garner P and **Flynn EV**. (2000) Assessing the potential for bias in meta-analysis due to selective reporting of subgroup analyses within studies. Statistics in Medicine, 19(24): 3325-3336. doi:10.1002/1097-0258(20001230)19:24<3325::AID-SIM827>3.0.CO;2-D

3.3. Hahn S, **Williamson PR** and Hutton JL. (2002) Investigation of within-study selective reporting in clinical research: follow-up of applications submitted to an LREC. Journal of Evaluation in Clinical Practice, 8(3): 353-360. doi:10.1046/j.1365-2753.2002.00314.x

3.4. Williamson PR, Gamble C, Altman DG, Hutton JL. (2005) Outcome selection bias in meta-analysis. Statistical Methods in Medical Research; 14(5): 515-524. doi:10.1191/0962280205sm415oa

3.5. Dwan K, Altman DG, Arnaiz JA, Chan AW, Decullier E, Dickersin K, Easterbrook PJ, Von Elm E, Gamble CL, Ghersi D, Ioannidis JPA, Simes RJ, **Williamson PR**. (2008) Systematic review of the empirical evidence of publication bias and outcome reporting bias. PLOS ONE 3(8):e3081. doi:10.1371/journal.pone.0003081

3.6. Gargon, E, Gurung, B, Medley, N, Altman, D, Blazeby, J, Clarke, M, & **Williamson, P.** (2014). Choosing important health outcomes for comparative effectiveness research: a systematic review. Value in Health, 17(7), A435. doi:10.1016/j.jval.2014.08.1118

4. Details of the impact

This body of research conducted by mathematicians at the University of Liverpool exposed fundamental problems with bias in outcome selection and reporting across the global multibillion (US) dollar clinical trials sector **[3.1-5]**. Accordingly, Prof Williamson launched the COMET Initiative (**C**ore **O**utcome **M**easures in **E**ffectiveness **T**rials) at Liverpool in January 2010, the COMET website in 2011 and populated the open access COMET database in 2014, to introduce standardisation of outcomes in clinical trials **[5.1]**. Standardisation is vital for ensuring results from different trials can be compared, combined and made relevant to patients for better informed decisions about treatments, and to robustly establish which treatments work.

The COMET database brings together 722 minimum outcome sets **[5.1a]** that should be measured and reported in all clinical trials for particular conditions (**C**ore **O**utcome **S**ets – COS) in a dedicated and unique global repository. Since August 2013, with Prof Williamson as Chair **[5.1b]**, COMET has been adopted by at least ten key healthcare decision-making organisations **[5.2, 5.3, 5.4a, 5.5, 5.6, 5.7a, 5.7d-f, 5.8]**, including the National Institute for Health and Care Excellence (NICE) and other regulators, funders and pharmaceutical companies in the UK, Europe and the US, and has transformed public participation in outcome-setting **[5.1c]**. These societal **[4.1]** and policy impacts **[4.2-5]** are described below.

4.1. Establishing patient involvement

Up to August 2013 only 16% (31/198) of all published COS involved the public **[3.6]**, rising to 93% (303/325) of all COS in development by October 2020 **[5.1c]**. The Irish Neonatal Health Alliance charity explains how the COMET Initiative has been '*instrumental in ensuring COS embody outcomes that matter most to patients*' **[5.9]**. Through its People and Patient Participation group, COMET has established a patient voice in COS development that did not previously exist, and made this standard practice across the clinical trials sector. Mechanisms include a video animation explaining COS first published March 2018, translated by request into twelve languages **[5.1d]**. Global pharmaceutical company UCB Pharma Ltd uses COMET's resources to explain COS to their patient partners **[5.8]**. A patient participant with diabetes describes feeling '*empowered*', and having his opinions valued as '*simply amazing*' **[5.1e]**.

4.2. Making clinical guidelines more robust

COMET is improving recommendations for clinical practice. Since 2014, NICE has incorporated COMET into its clinical guidelines **[5.2a,b]**. NICE has since developed and published more than 150 clinical guidelines which health professionals in England must take fully into account. NICE describes COMET as '*an excellent resource for NICE guideline developers to check whether there is a COS relevant to a guideline they are developing*' **[5.2a]**. NICE also uses COMET to trigger guideline updates (since 2016) **[5.2a]**, in digital health technologies guidance (2019) **[5.2c]**, and in guidance for the life sciences industry developing medicines for COVID-19, in which the use of COMET is '*strongly recommended*' (2020) **[5.2d]**. NICE explains how '*COMET is establishing consistency in outcome selection across COVID-19 clinical trials, meaning that urgently-needed trial data can easily be combined and compared for robust decision-making about the best possible treatments for COVID-19'* **[5.2a]**. NICE also uses COMET to identify outcomes for use in NICE Quality Standards, helping to ensure measures that '*matter most for patients and service users'* **[5.2a]**.

Overall, NICE values COMET's '*commendable achievements in improving the robustness of assessment of health care interventions for clinical guidelines in England'* **[5.2a]**.

The equivalent of NICE in Sweden, the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) cites inconsistent outcomes as '*…one of the most common reasons clinical trial results cannot be combined, leading to inconclusive evidence for effectiveness… Resulting guideline recommendations lack clarity and robustness, which increases variability in clinical decision-making and patient access to the best possible*

treatments.' **[5.3]**. Since 2019 SBU has used COMET to check for COS in production of approximately 15 assessments annually **[5.3]**. SBU recognises how COMET has '*successfully spread the usefulness of COS to key stakeholders such as researchers, HTA* [Health Technology Assessment] *organisations, funders and patient organisations*', describing the COMET database as '*the internationally accepted tool for easy access to COS and is therefore a critical resource for guideline developers'* **[5.3]**.

4.3. Required by regulators

The UK Health Research Authority best practice guidance for clinical trial design sets out '*an expectation that the core outcomes will be collected and reported'* using COMET **[5.4a]**. The UK's main trial registry ISRCTN, recognised by the World Health Organisation (WHO), states users should consult COMET **[5.5a]**. The ISRCTN registry processed 7,943 trials for the six year period from August 2013 to July 2020, including 5,826 trials that are now completed **[5.5b]**.

The US-based Clinical Data Interchange Standards Consortium describes COMET as '*an essential tool for transforming how key outcomes data is collected, analysed and reported consistently around the globe'* and is '*enabling the application of agreed standardised core outcome sets (COS) in global data standards'* **[5.6]**. These data standards are mandated for submissions to the national drug licensing authorities in the US and Japan.

COMET is explicitly welcomed by the Senior Medical Officer of the European Medicines Agency **[5.1f]**, with their Paediatric Network reporting how COMET '*has contributed significantly to the assessment of medicines in paediatrics',* recognising *'its positive impact on the clinical trials sector'* **[5.10]**.

4.4. Changing government funding guidelines

The Director of the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme – the UK's largest government-funded programme of clinical trials – explains why COMET is important to funders: *'As a funder I see it as our duty to promote the use of core outcome sets so that the results of our publicly funded clinical trials can be compared and combined with other trials'* **[5.1g]**. NIHR funding guidelines require applicants to use the COMET database **[5.7a]**. Between April 2015 and March 2019, this guidance underpinned 1,557 applications for Health Technology Assessment funding, resulting in 320 funded trials **[5.7b]**. NIHR guidance for COVID-19-related funding (March 2020) states: '*it is critically important to include the relevant core outcome sets for COVID-19 as indicated on the COMET website*' **[5.7c]**.

Equivalent major funders in Ireland **[5.7d]**, Belgium **[5.7e]** and the US **[5.7f]** have adopted COMET in their guidelines.

4.5. Setting new standards for industry

COMET is enabling the pharmaceutical industry to select and report consistent outcomes for commercially funded clinical trials, in which companies globally invest tens of millions of (US) dollars. Consistent outcomes ensure trials are relevant to patients and serviceable for other decision-makers such as NICE. In 2018, the *Big Data for Better Outcomes* toolkit was developed by a consortium of the world's largest pharmaceutical companies, including GlaxoSmithKline, Pfizer, Roche **[5.4b]**. This toolkit cites the COMET database throughout, as best practice in commercial trials **[5.4b]**.

The *Standard Protocol Items: Recommendations for Interventional Trials*, 'SPIRIT' statement is an international framework for clinical trials that incorporates COMET. Between August 2013 and December 2019, approximately 699 new trial protocols used this framework **[5.4c]**, which is

endorsed by the Association of the British Pharmaceutical Industry, GlaxoSmithKline and Janssen Pharmaceutical Companies of Johnson & Johnson **[5.4d]**.

Global pharmaceutical company UCB Pharma Ltd uses the COMET database to '*determine what outcomes we should consider setting for our [commercial] trials*', describing COMET's mission as '*essential*' **[5.8]**.

5. Sources to corroborate the impact

5.1. COMET website. **a)** COMET database search results showing 722 COS (20th October 2020). **b)** Prof Paula Williamson Chair of the COMET management group. **c)** COMET database search results showing 303/325 (93%) patient participation (20th October 2020). **d)** What are core outcome sets? A COMET Initiative animation for patients (March 2018). **e)** COMET patient participation webinar *No Choice of Outcomes About us Without us!* (February 2020). See *Part 2: Patient perspectives on involvement in core outcomes sets* (4:38 to 5:02 minutes). **f)** Video interview (October 2018) with the Senior Medical Officer, European Medicines Agency (EMA). See 3:38 to 3:55 minutes. **g)** Podcast (April 2018) by the Director of the National Institute for Health Research (NIHR) Health Technology Assessment Programme. See 1:45 to 2:11 minutes.

5.2. Evidence from The National Institute for Health and Care Excellence (NICE). **a)** Letter from the Associate Director and Senior Technical Adviser, Centre for Guidelines, NICE. **b)** 'Developing NICE guidelines: the manual': PMG20 (October 2014, updated October 2020). See p.32, 60 and 233. **c)** 'NICE Evidence standards framework for digital health technologies' (March 2019). See p.22. **d)** 'NICE and NIHR Evidence collection guide for medicinal products to prevent or treat COVID-19' (June 2020). See pp.3-4.

5.3. Letter from the Head of Department Evidence synthesis and assessment at the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU).

5.4. Industry best practice guidance. **a)** Health Research Authority (HRA) best practice guidance for clinical trial design (UK) (February 2019). **b)** Innovative Medicines Initiative (IMI) Big data for better outcomes (BD4BO) (2018). *A Practical Toolkit for the identification, selection and measurement of outcomes including in real-world settings* See for example pp.4,8,14,15,18. **c)** Estimate using data from the SPIRIT website of the number of published protocols using the framework between August 2013 and December 2019. **d)** Industry endorsement of the SPIRIT standard including the Association of the British Pharmaceutical Industry, GlaxoSmithKline and Janssen Pharmaceutical Companies of Johnson & Johnson (SPIRIT website).

5.5. International Standard Randomised Controlled Trial Number (ISRCTN) trial registry. **a)** COMET listed under ISRCTN registry outcomes data item definitions. **b)** ISRCTN registry search results for the number of trials registered between August 2013 and July 2020.

5.6. Letter from the Vice President, Development Opportunities for the Clinical Data Interchange Standards Consortium (CDISC).

5.7. Government funding guidelines. **a)** National Institute for Health Research (NIHR), Health Technology Assessment guidance notes (May 2019). *See 'project plan'.* **b)** NIHR Health Technology Assessment success rates showing number of proposals submitted and accepted. **c)** NIHR Guidelines for Covid-19 support (March 2020). See 'Apply' section. **d)** Health Research Board (HRB, Ireland) Definitive Interventions and Feasibility Awards (DIFA) guidance notes (May 2020). See p. 29. **e)** Health Care Knowledge Centre (KCE, Belgium). Guidance notes for trial programme (June 2020). See application form/guidance notes, p.7. **f)** US Patient Centred Outcomes Research Institute (PCORI) Covid-19 funding announcement (May 2020). See p.5.

5.8. Letter from the Global Head of Real World Data & Policy, UCB Pharma Ltd.

5.9. Letter from Director of Advocacy and Policymaking for the Irish Neonatal Health Alliance (registered charity).

5.10. Letter from the Co-Chairs of the European Network of Paediatric Research, European Medicines Agency (EMA).