Institution: University of East Anglia

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Enhancing the methodology for identifying and prioritizing adverse effects data in clinical trials and systematic reviews of healthcare interventions

Period when the underpinning research was undertaken: 2007-2020

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:
Yoon K Loke	Professor	2003 – to present

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Prof. Loke's pioneering work has resulted in:

(i) The development of best methods for assessing adverse events in clinical trials and systematic reviews and
(ii) The accurate recording of mortality for COVID-19.

For adverse effects his work stimulated Agencies in the US, Europe and Australia to issue new guidance on best methods for identifying and prioritizing reports of harms. Practical implementation led to the World Health Organization issuing more cautious guidelines for high oxygen use during surgery. For COVID-19 his work uncovered limitations in how Public Health England's compiled mortality data, leading to a revised figure of over 5000 fewer deaths.

2. Underpinning research

Adverse effects (AE) of drugs are a major international burden worldwide, causing 6.5% of hospital admissions. In NHS hospitals, the cost is estimated at GBP84,000,000 with 627 lives lost due to AE per year. Although most AEs may seem minor (e.g., muscle aches) these may profoundly impact people's daily life and may deter them from taking recommended medications such as statins.,

However, Professor Loke's research programme at UEA from 2003 onwards revealed two key deficiencies:

(i) Adverse effects were poorly reported and difficult to identify in publication of clinical trials, and
(ii) This had the knock-on consequences of creating major difficulties for detection and quantification of adverse effects in systematic reviews of healthcare treatments.

Other researchers have demonstrated that adverse effects were not covered in 37/80 (46%) of NIHR health technology evaluations. When harms are relegated to low priority topics, we are stuck with biased research where benefits of therapy are over-emphasized, but risks are downplayed or concealed.

Professor Loke's research programme, in conjunction with his role as a founder member of the Cochrane Adverse Effects Methods Group was the first to re-dress this imbalance. This involved development of step-by-step methodological techniques for systematic reviews

(i) Prioritization of AE so that benefits and harms can be correctly weighted up
(ii) Choosing the most appropriate types of studies for reviews of AE
(iii) Best methods for searching and identifying studies so that comprehensive AE dataset is successfully acquired

The newly developed and first-ever structured framework for the AE assessment was published in 2007 [(1), cited by >80 systematic reviews to date (Scopus database)]; this guidance was also accepted as a new chapter in the Cochrane Handbook, a world-renowned and definitive source of methodological best practice.

The key steps were to formally quantify deficiencies in reporting of adverse effects in clinical trials and systematic reviews. Professor Loke's methodological study revealed substantial reporting bias with a high frequency of missing or partially reported adverse events (248/393 trials and observational studies failed provide full reports) (2) Prof. Loke subsequently demonstrated that 75% of analyses would be able to generate more accurate figures by accessing unreported or unpublished data (3). From this work, one main conclusion was "The declaration of important harms and the quality of the reporting of harm outcomes must be improved in both primary studies and systematic reviews" (3). This work led to Professor Loke being invited to take a pivotal role in the Steering Group for constructing the PRISMA-Harms checklist, an internationally recognized reporting guideline to improve harms reporting (4).

Overall, Prof. Loke's research programme has focused on addressing serious deficiencies in evaluation of AEs and developing best methods for accurately measuring harm:

(i) Assessing risk of missing data and the optimal methods of overcoming this through use of relevant and appropriate data sources
(ii) Empirically developing and testing search strategies that can reliably identify AE data (5)
(iii) Prioritization and explicit reporting of AE in trials and systematic reviews to enable balanced assessment of benefit vs. harm.

In view of Prof. Loke's expertise in assessing benefit:harm, the World Health Organization (WHO) approached Prof. Loke and commissioned an evaluation into adverse effects of oxygen in surgical settings. This was because other experts and clinicians had raised serious safety concerns (Guardian UK newspaper Feb 2018) regarding the WHO's recommendations on oxygen therapy. Hence, Prof. Loke was able to demonstrate the practical value of implementing his benefit:harm framework in systematic reviews assessing efficacy and safety of oxygen for preventing surgical site infections (5).

In collaboration with the University of Oxford Prof. Loke applied his expertise in measurement of adverse events to COVID-19 related deaths. He identified marked discrepancies between Public Health England (PHE)-compiled data as compared to NHS hospital and Office of National Statistics data (6). Prof. Loke discovered that anyone who has tested COVID positive but subsequently died at a later date of any cause will be included on the PHE COVID death figures. By this PHE definition a patient who has tested positive, but successfully treated and discharged from hospital, will still be counted as a COVID death even if they had a heart attack or were run over by a bus three months later (6). In order to fix this statistical flaw that led to an over-exaggeration of COVID-associated deaths in England, implementation of a clearly-defined time period after a positive COVID-19-test was recommended.

3. References to the research

(UEA authors highlighted in **bold**)

1. Systematic reviews of adverse effects: framework for a structured approach.
Loke YK, Price D, Herxheimer A.
BMC medical research methodology (**2007**); 7(32). DOI: 10.1186/1471-2288-7-32

2. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews.
Saini P, **Loke YK**, Gamble C, Altman DG, Williamson PR and Kirkham JJ.
BMJ. (**2014**); 349:g6501, DOI: 10.1136/bmj.g6501

3. Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review.

Golder, S., **Loke, YK.**, Wright, K., Norman, G.
PLoS Medicine (**2016**); 13(9): e1002127. DOI: 10.1371/journal.pmed.1002127

4. PRISMA harms checklist: improving harms reporting in systematic reviews.
Zorzela L, **Loke YK**, Ioannidis JP, Golder S, Santaguida P, Altman DG, Moher D, Vohra S; PRISMA Harms Group.
BMJ. (**2016**); Feb 1;352:i157. DOI: 10.1136/bmj.i157

5. Safety of 80% vs 35% fraction of inspired oxygen in patients undergoing surgery: a systematic review and meta-analysis.
Mattishent, K., **Thavarajah, M.**, **Sinha, A.**, **Peel, A.**, Egger, M., Solomkin, J., de Jonge, S., Latif, A., Berenholtz, S., Allegranzi, B., and **Loke, YK.**
British Journal of Anaesthesia. (**2019**); 122(3) pp.311-324. DOI: 10.1016/j.bja.2018.11.026

6. Why no one can ever recover from Covid-19 in England.
Loke, YK., Heneghan, C.
The Spectator. Published 17 July (**2020**). Available online at:
https://www.spectator.co.uk/article/why-no-one-can-ever-recover-from-covid-19-in-england.

4. Details of the impact

When Prof. Loke's 2007 AE framework was first published, there were just under 80 systematic reviews in 2007 that focused on evaluating AE. By the year 2014, this had seen a more than four-fold jump with 348 systematic reviews focusing on AE. Since publication of the PRISMA-Harms checklist in 2016, more than 75 systematic reviews have cited PRISMA-Harms as an underlying basis for the methods in their review. This includes a very recent review on COVID-19-related adverse events (e.g., miscarriage, foetal mortality) in pregnant mothers.

Methodological advances in the process of evidence synthesis for detailed assessment of harms: New technology or process has been adopted by the US Government Agency for Healthcare Research and Quality (AHRQ) [Source A]

Professor Loke's work led to new AHRQ methodological guidance to prioritize and select harms in their evidence-based reviews of healthcare interventions. This ensures that balanced assessments are available for those who commission and use information from systematic reviews in the US and internationally.

The AHRQ is part of the Department of Health and Human Services and is the lead US Federal department charged with improving the safety and quality of America's health care system. It has a USD451,000,000 budget to develop the knowledge, tools, and data needed to improve the health care system and help patients, clinicians and policymakers make informed health decisions. The AHRQ's overarching objectives are to produce evidence to make health care safer and of higher quality and they have produced more than 700 systematic evidence-based reviews in the past 20 years. Notable current examples in progress include masks for prevention of COVID-19, and no-touch disinfection modalities.

In Feb 2016, the AHRQ contacted Prof. Loke to arrange an interview and provide written expert advice into their methodological guidance for assessing adverse effects. The AHRQ emphasised that the selection and prioritization of harms:

> *"was identified as an important area given the potentially large number of harms that could be assessed in many reviews."*
> [Source A page 23]

Here, the AHRQ had recognized the incomplete benefit:harm coverage in their evidence-based reviews, particularly when they became aware of Prof. Loke's published data regarding selective and incomplete reporting on harms (2,4). Hence the AHRQ set up interviews with key experts/informants by invitation and incorporated Prof. Loke's expertise into their Methods guide

to explicitly identify harms, and to select specific harms for evaluation in AHRQ evidence-based reviews.

This led to the publication in Feb 2018 of the updated AHRQ Methods Guide for Comparative Effectiveness Reviews: Prioritization and Selection of Harms for Inclusion in Systematic Reviews [Source A].

Methodological recommendations on best way to search for and identify reports of adverse effects (European Medicines Agency, Australian National Health and Medical Research Council) [Sources B and C]

The European Medicine Agency (EMA) set up the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCEPP) in 2007. This network gives methodological guidance to public institutions and commercial research organisations across all of Europe on the standards they should adhere to when conducting pharmacoepidemiology studies with safety outcomes. Prof. Loke's systematic framework and terms used in the search (5) are explicitly cited and form the basis for ENCEPP Methodological Standards on how to conduct comprehensive reviews of safety [Source B]. Similarly, the Australian National Health and Medical Research Council has drawn up methodological standards on identification of evidence [Source C], and they cite Prof. Loke's research (4) into missing adverse effects data as the basis for explicit recommendations to search for and include data from grey literature.

Empirical use of this new benefit:harm methodology has led to policy changes in recommendations of treatment by the World Health Organization [Source D]

Surgical site infections are a major burden internationally affecting up to 300 000 patients per year in the USA, costing between USD3,500,000,000 and USD10,000,000,000. Previous WHO 2016 guidelines made a Strong Recommendation for high inspired oxygen to reduce wound infections. However, this was widely challenged and publicly debated by the clinical community who had major reservations about safety of oxygen and incomplete evaluation of benefit:harm balance. Prof. Loke was invited by the WHO to take part in the conduct of two new systematic reviews (one on benefit, the other focusing on harm). The two reviews yielded a far more complete understanding of the clinical effects of oxygen and the limitations of the underlying data in terms of bias and inadequate measurement of outcomes. Both reviews (with Professor Loke as co-author) generated new and more comprehensive benefit:harm evaluations for the December 2019 re-written WHO Global Guidelines for the Prevention of Surgical Site Infection. The two reviews are specifically listed as the evidence-base for the more carefully nuanced updated recommendations. Here, incorporation of Prof. Loke's new methodologies for assessing benefit and harm led to the WHO down-grading the recommendations for high oxygen delivery in surgical patients, particularly in developing countries where oxygen is scarce [Source D]. Now that WHO is no longer making a strong recommendation for high oxygen concentrations in surgical patients, the clinicians in developing countries are able to prioritize scarce supplies oxygen for use in COVID-19 patients.

UK government reviewed and revised their definition of COVID-19-mortality in August 2020 following publication of Prof. Loke's evaluation [Sources E, F and G]

Prof. Loke's analysis of COVID-19 -deaths triggered a review of PHE's method of data collection which was ordered by the Secretary of State for Health on that very same day [Source E]. The review of PHE's method of data collection was reported globally thousands of times in just two days between 17-19th July [Source F]. The review reported its findings on 12 Aug 2020, with PHE revising its method of measurement to report both: (i) deaths within 60 days or if the death occurred after 60 days, COVID-19 is listed on the death registration and (ii) deaths in laboratory-confirmed positive individuals where the death occurred within 28 days. The four Chief Medical Officers across the UK also agreed on the standardised measurement of COVID-19-related deaths to a defined time-period of 28 days within a positive test allowing direct comparisons of mortality rates. The death toll in England was revised down by 5,377 to 41,329 [Source G]. The

greatest impact of Prof. Loke's recommendation was seen for mid-July, where the death toll for England was drastically revised down by 75% from 442 to 111 [Source H, table 2]. The standardised definition of COVID-19 deaths also allows compatibility with WHO international datasets: England is no longer an outlier (the WHO definition specifies "There should be no period of complete recovery from COVID-19 between illness and death"). A quote from the Director of Health Improvement at PHE emphasises the importance of the revised method:

> *"Our analysis of the long-term impact of the infection now allows us to move to new methods, which will give us crucial information about both recent trends and overall mortality burden due to Covid-19"*
> [Source G]

5. Sources to corroborate the impact

A. AHRQ report - Prioritization and Selection of Harms for Inclusion in Systematic Reviews. Methods Guide to Comparative Effectiveness Reviews. February 2018.

B. European Network of Centres of Pharmacoepidemiology and Pharmacovigilance. ENCePP Guide on Methodological Standards in Pharmacoepidemiology: Annex 1. Guidance on conducting systematic reviews and meta-analyses of completed comparative pharmacoepidemiological studies of safety outcomes. European Medicines Agency. Last updated: 04 July 2019

C. NHMRC. Guidelines for Guidelines: Identifying the evidence. Last published 6 September 2019

D. Global guidelines for the prevention of surgical site infection, second edition. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

E. The Guardian article: Matt Hancock orders urgent review of PHE Covid-19 death figures. 17 July 2020. (Downloaded from theguardian.com December 2020)

F. Media report of PHE review (20 July 2020)

G. The Financial Times article: UK death toll revised down by 5,377 after data review. New methodology of counting daily figures brings England in line with rest of nation. 12 August 2020, article available on-line at ft.com

H. Public Health England. PHE Reporting of COVID-19 deaths: technical summary – 12 August 2020. (Table 2)