EDITORIAL

Doug Altman's legacy to Cochrane and evidence synthesis

Jonathan J Deeks, Sally Hopewell, David Moher, Julian PT Higgins, Karel GM Moons, Jackie Chandler, Gerd Antes

Cochrane Database of Systematic Reviews 2018;(9):ED000127 **https://doi.org/10.1002/14651858.ED000127**

Publication date: 14 September 2018

It is hard to find an area of medicine or health research where the initiatives Doug Altman instigated and championed have not had an influence. Doug was a man on several missions: advocating statistical peer review to reduce statistical errors in medical journals; improving doctors' and health researchers' understanding of statistics and research design through thoughtful teaching; writing accessible and well-used statistical notes; producing a major medical statistics textbook; advocating a focus on estimating effects and confidence intervals rather than hypothesis testing; and providing numerous templates and guidelines to educate journals and researchers as to how they should report their studies.[1][2][3][4][5][6] Doug was one of the leaders of the COMET Initiative, promoting the development of core outcome sets to be measured and reported in all randomized trials of a specific condition, making it easier for the results of trials to be compared, contrasted, and combined as appropriate.[7] He also pushed for the development of reviews for prognostic research. His dedication to his work continued until a few days before he died.

Doug first encountered meta-analysis in the late 1970s. The idea of combining results from multiple studies chimed with his growing concerns that most trials were too small to have adequate power to detect a worthwhile clinical difference and that sampling variation would lead to differences in repeated studies.[8] Ten years before the creation of The Cochrane Collaboration, Doug lectured on this topic and wrote (but never quite finished) a comprehensive paper that anticipated many developments in the field.[9]

Doug was involved in Cochrane from the start. He and Iain Chalmers had worked together in the editorial team at the *British Journal of Obstetrics and Gynaecology* during the 1980s. In 1993, Iain recruited Doug, together with Ken Schulz, to chair a meeting in Oxford to flesh out the statistical methods required for the emerging Cochrane Collaboration. The meeting debated and made recommendations on effect measures, heterogeneity, fixed- and random-effects models, and analysis of continuous data-topics that dominated statistical discussions in subsequent years. The meeting's report concluded with a list of ''Implications for consideration by The Cochrane Collaboration (not necessarily formed through unanimous agreement)'' and scoped out a plan for the functionality of the Collaboration's original statistical software and content of the statistics section of the first version of *The Cochrane Reviewers' Handbook* (now called the *Cochrane Handbook for Systematic Reviews of Interventions*).[10] Doug and Iain Chalmers also edited an early book on systematic reviews, with contributions from many other notable authors.[11]

Doug and others realized that it was important to involve statisticians to ensure Cochrane's success, and that plans be put in place for a programme of methodological research to inform the systematic review process and address the questions raised in the 1993 meeting. In 1995, Doug (with Ken Schulz) founded the Cochrane Statistical Methods Group, which he led for 20 years. The long-term success of the Statistical Methods Group owes much to Doug's natural openness, his ability to identify the most important research questions and to challenge statistical dogma, his intolerance of poor scientific method, and his willingness to work with all who showed interest. From the outset, he engaged an international team of statisticians, set an open agenda for methods research and debate, and created an atmosphere and approach that encouraged early-career as well as established statisticians. Many are indebted to the opportunities created by Doug's warm welcome to the group.

Doug made important contributions to many meta-analytical projects, including measuring and investigating heterogeneity and inclusion of cross-over trials in meta-analysis.[12][13][14][15][16] However, he later commented that ''the precise statistical approach is generally a relatively unimportant consideration in comparison with the wider contextual issues''.[8] This reveals where Doug's most impactful and lasting contributions to trials (and to both systematic reviews and Cochrane) were probably made: most notably the assessment of risk of bias and challenges created by missing information. These he achieved by leading the way in creating evidence-based reporting guidelines, such as CONSORT and PRISMA, and amassing the scientific evidence that forms their

empirical basis.[17][18]

Initially working with Ken Schulz, but later with many others, Doug championed an approach (later called 'meta-epidemiology') whereby the results of cohorts of trials are re-analysed to learn how features of their design and analysis affect their findings.[19] The content of the *Cochrane Pregnancy and Childbirth Database* and subsequently the *Cochrane Database of Systematic Reviews* provided rich opportunities to perform such work, exploiting their broad scope and standardized electronic structure. This created a virtuous circle whereby the work of past Cochrane reviewers provided the evidence to improve Cochrane methods, feeding into guidance for future reviewers. The initial findings emphasized the importance of allocation concealment (the source of the term is discussed in one of Doug's very last papers) and other aspects of trial design, which were built into Cochrane's risk of bias assessment.[20][21] Further projects investigated publication bias and selective reporting of outcomes, influencing the development of core outcome sets, appreciating the importance of pre-specification of outcomes, and encouraging the publication and open availability of trial protocols.[22][23][24][25]

Of course, reporting guidelines also benefit systematic reviewers, as they ensure that future trials report study details and results in ways that facilitate their easier inclusion in systematic reviews and meta-analyses. More importantly, reporting guidelines teach researchers not only how to report research, but also the requirements and rationale for good study design, execution, and analysis.

In 1994, Doug memorably wrote: ''We need less research, better research, and research done for the right reasons''.[26] This quote comes from his article 'The scandal of poor medical research', which was often referenced in the week following his death and was downloaded 34,000 times on the day he died. Doug worked on reporting guidelines before the publication of the CONSORT Statement, first published in 1996 and updated in 2001 and 2010.[27][28][29] CONSORT has been translated into 13 languages, and there are extensions for reporting of different types of trial designs, interventions, and outcome data. The first version of CONSORT received Doug's typical laser-focused peer review: he recommended an accompanying instructive document to facilitate the dissemination and uptake of the guideline. So, Doug led the extensive development of the 2001 CONSORT explanation and elaboration article (CONSORT E&E).[30] The main CONSORT paper, cited more than 15,000 times, is ranked among the most highly cited scientific contributions of all time, and hundreds of biomedical journals endorse CONSORT.

Doug was inspirational and influential in the development of another Methods Group in Cochrane: The Reporting Bias Methods Group (now the Bias Methods Group), leading the group for more than 20 years. The QUOROM Statement,[31] an early guidance for reporting meta-analysis of randomized trials, was further advanced when Doug joined the executive group of the PRISMA initiative (Preferred Reporting Items of Systematic reviews and Meta-Analyses), along with another Cochrane giant, the late Alessandro Liberati. The PRISMA Statement was published in 2009, and Alessandro used Doug's CONSORT E&E template to develop the PRISMA E&E.[32][33] Doug's strong leadership in advocating reporting guidelines to improve the quality of published research culminated in 2006, when he founded the EQUATOR Network, the first global organization dedicated to improving health research and reporting practices.[34] Doug was also instrumental in helping to develop one of the early EQUATOR products: the first guidance on how to develop reporting guidelines.[35]

Over the last 30 years, Doug was also instrumental in improving prognosis research, for both primary and meta prognosis studies. As with all Doug's interests, this passion began early in his career. In the 1980s he was involved in various applied studies of prognostic factors and prognostic models in patients with liver disease and cancer. In 1994 he wrote with Richard Simon the seminal paper 'Statistical aspects of prognostic factor studies in oncology', which addressed more than statistics.[36] It provided suggestions to improve the validity and accurateness of the design, conduct, analysis, and reporting of primary prognosis research, and addressed the importance of meta-analysis of prognostic studies. Subsequent decades saw many more guidance papers,[37][38][39][40][41][42] followed by a series of articles on the design, conduct, and analysis of prognostic model research, the PROGRESS series on the four types of prognosis research, and more recently the plea for transparency in prognosis research and the TRIPOD reporting guideline.[43][44][45][46]

In 2001 Doug remarked: ''Systematic reviews are applicable to all types of research design, and prognostic studies are an important additional area where appropriate systematic review methodology should be applied''.[47] Furthermore, he noted, ''meta-analysis of prognostic studies using individual data from patients may overcome many of the difficulties [of reviews based on aggregate data only]''. This notion needs to become common practice, certainly in the current era of open science and data sharing.[45] This vision for systematic reviews of prognosis studies led to yet another Cochrane Methods Group, for methods of prognosis research.[48] Again, Doug was inspirational in setting up and actively contributing to this group. Its convenors will continue to work with his ideas to enhance the design, conduct, and reporting of reviews of prognosis studies, and the Group is currently engaged in the implementation of Cochrane Reviews of prognosis.

Doug often brought discussions back to a focus on the needs of patients, and his career was ultimately driven by the tenet that *bad research is not good for patients*. The developments described here only mattered because they led to better research that better informed the care of patients. Doug never hesitated to call out poor research, publication practices, conflicts of interest and the perverse incentives of academia, where he judged that they compromised the evidence needs of patients. His guidance papers and lectures stimulated numerous PhD theses, research projects, fellowship applications, and indeed entire careers. Among the many tributes to Doug, one aspect not highlighted is his love of acronyms (''You can't

 | https://doi.org/10.1002/14651858.ED000127
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do good research without a good research acronym''), and he spent many happy hours creating acronyms for reporting guidelines (STROBE, TRIPOD, SPIRIT, and STARD, to name but a few). Doug was too modest, too aware that he was only one player in a team, and probably also too much of a biostatistician, ever to correlate improvements in research with his efforts or to claim personal achievements. We have less hesitation in doing this. Doug, we have no doubt that you have left the world a better place for patients.

Finally, we say farewell to Doug Altman, who will live in the thoughts, hearts, and output of many, and whose legacy will continue to inspire generations of researchers. He will be deeply missed by us all.

Author information

Jonathan J Deeks[1], Sally Hopewell[2], David Moher[3], Julian PT Higgins[4], Karel GM Moons[5], Jackie Chandler[6], Gerd Antes[7,8]

[1]Institute of Applied Health Research, University of Birmingham, UK. [2]Oxford Clinical Trials Research Unit, University of Oxford, UK. [3]Ottawa Hospital Research Institute, University of Ottawa, Canada. [4]Population Health Sciences, Bristol Medical School, University of Bristol, UK. [5]Julius Center for Health Sciences and Primary Care and Cochrane Netherlands, UMC Utrecht, Utrecht University, The Netherlands. [6]Editorial & Methods Department, Cochrane, London, UK. [7]Institute for Evidence in Medicine (for Cochrane Germany Foundation), Albert-Ludwigs-University, Freiburg i.B., Germany. [8]Cochrane Germany Foundation, Freiburg i.B., Germany

Declarations of interest

The authors have completed the ICMJE form for disclosure of potential conflicts of interest (forms available on request). The authors have nothing to disclose.

Provenance and peer review

This editorial was commissioned and was not externally peer reviewed.

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